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Ovarian Cancer Screening in the General Population

**Thesis submitted for the degree of Doctor of
Medicine at the University of London**

2007

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1 ABSTRACT

Despite significant improvements in therapy, ovarian cancer continues to be a leading cause of death amongst women with gynaecological malignancies. Advanced stage at diagnosis is thought to be a major contributor to mortality. Hence, there is considerable interest in early detection through screening.

In the 1990s, Professor Jacobs pioneered the development of a multimodal ovarian cancer screening (OCS) strategy using serum CA125 as the first line screen and pelvic ultrasound as the second line test. This thesis summarises the next steps in the journey with refining of the screening algorithm, feasibility testing in a pilot randomised control trial (RCT) and finally setting up and recruiting 200,000 women into the largest ever RCT .

The risk of ovarian cancer in postmenopausal women with elevated CA125 levels was established through a detailed analysis of 1219 pelvic scans from 741 women with raised CA125 levels in the completed trial of 22,000 women. Based on this, the multimodal 'Risk of Ovarian Cancer' (ROC) algorithm was refined and morphology instead of volume was used to interpret the ovarian scans.

The refined ROC algorithm was then prospectively evaluated in a pilot RCT of 13,582 postmenopausal women. The trial established that screening

using the ROC algorithm was feasible and could achieve high specificity and positive predictive value.

The improved performance characteristics of the screening strategy and the experience accumulated in running and organising the pilot trial led to the design and successful implementation of a RCT - the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) - to assess the impact of early detection on disease mortality. The trial commenced in 2001 with recruitment of 202,638 postmenopausal women by September 2005. The issues involved in setting up the trial, recruitment of 202,000 women and the baseline characteristics of this population are described.

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5 DECLARATION

I declare that this thesis has been composed and the work described in it performed by the candidate Dr Usha Menon. It has not been submitted for another degree either at this or at another university. All sources of information have been acknowledged.

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7 COMMONLY USED ABBREVIATIONS

Abbreviation	Phrase
CC	Coordinating centre
CGH	Comparative Genomic Hybridisation
CR UK	Cancer Research UK
CRUK	Cancer Research UK
DMEC	Data Monitoring and Ethics Committee
DMS	Data management system
DOB	Date of Birth
FLEXISIG	UK Single Flexible Sigmoidoscopy screening trial
GCP	Good clinical Practice
GP	General Practitioner
IQ	Inter quartile
MRC	Medical Research Council
NHS	National Health Service
NIH	National Institute of Health, USA
OC	Ovarian cancer
OCS	Ovarian Cancer Screening
ONS	Office for National Statistics
PCT	Primary Care Trust
RC	Regional centre
RCT	Randomised control trial
ROC	Risk of Ovarian Cancer
TMC	Trial Management Committee
TSC	Trial Steering Committee
WHI	Women's Health Initiative trial
MWS	Million Women Study
EOC	Epithelial Ovarian Cancer
TVS	Transvaginal ultrasound
PLCO	Prostrate Lung Colon Ovary Screening Trial
UKCTOCS	United Kingdom Collaborative Trial of Ovarian Cancer Screening
CT	Computerised Tomography
MRI	Magnetic Resonance Imaging
3D	Three-dimensional

8 LITERATURE REVIEW

8.1 Introduction

Ovarian cancer is the fourth most common cancer diagnosed in women in the UK. Nearly 6,600 new cases are diagnosed annually^{1 2} with a world wide incidence of over 190,000 new cases.³ The disease has a high mortality rate. It is the leading cause of death from gynaecological malignancies in the UK with nearly 4500 deaths annually and a case mortality to incidence ratio of 0.68.² There has been some improvement in disease outcome over the years with the age-standardised 5-year survival rate of patients diagnosed in the UK during 1996-99 rising to 36.4 (95%CI (35.6 - 37.2) months compared to 30.6 (95%CI 30.0 - 31.2) months in 1991-9.⁴ However there has been little decrease in the mortality rate especially in women over 50 years of age (Figure 8-1). This is in contrast to breast cancer where mortality rates have decreased by about 30% during the same time period.⁵ The data for the US shows similar trends (Figure 8-2)⁶.

8.2 Rationale for screening

The cancer is typically associated with vague, non-specific symptoms and over 75% of women have Stage III or IV disease at diagnosis.

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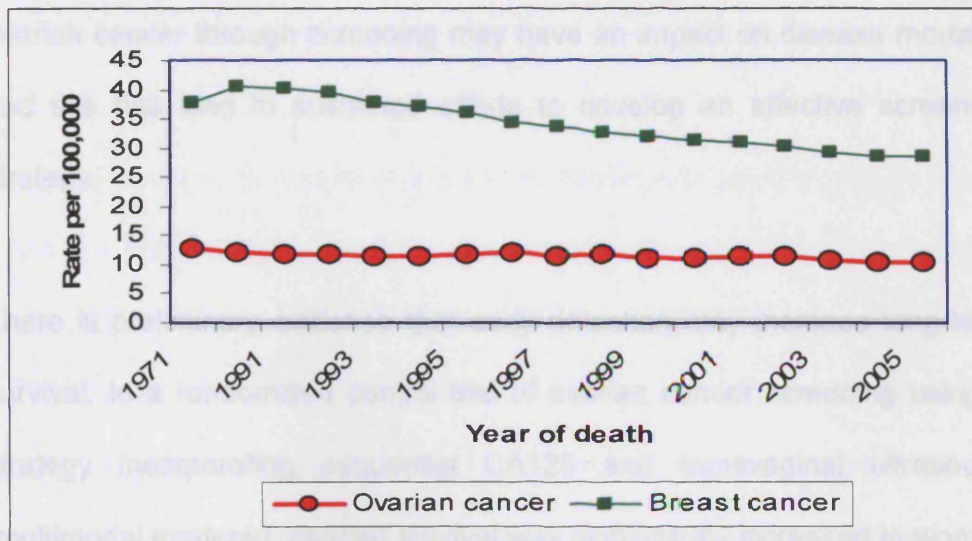


Figure 8-1: Age Standardised Mortality Rate for Ovarian and Breast Cancer England and Wales 1971-2005

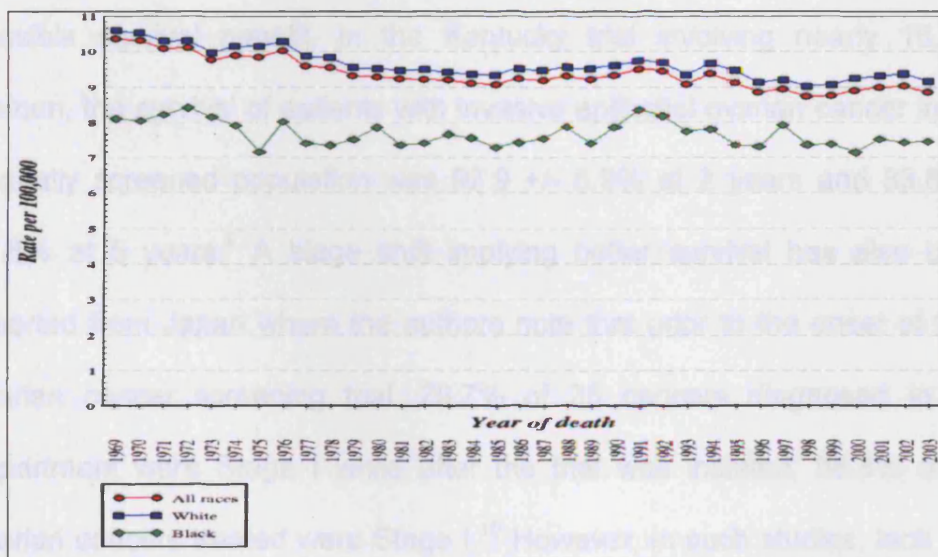


Figure 8-2 U.S. Age Adjusted Mortality Rate for Ovarian Cancer 1970-2000

The high mortality is believed to be a direct result of advanced stage at diagnosis, as early stage disease is associated with a 5-year survival of over

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80%.⁷ The link between stage and mortality suggests that early detection of ovarian cancer through screening may have an impact on disease mortality and this has led to sustained efforts to develop an effective screening strategy.

There is preliminary evidence that early detection may increase long-term survival. In a randomised control trial of ovarian cancer screening using a strategy incorporating sequential CA125 and transvaginal ultrasound (multimodal strategy), median survival was significantly increased in women with ovarian cancer in the screened group (72.9 months) when compared to the control group (41.8 months).⁸ Follow up data from prospective single arm ovarian cancer screening (OCS) trials also provide evidence of a possible survival benefit. In the Kentucky trial involving nearly 15,000 women, the survival of patients with invasive epithelial ovarian cancer in the annually screened population was 92.9 +/- 6.9% at 2 years and 83.6 +/- 10.8% at 5 years.⁹ A stage shift implying better survival has also been reported from Japan where the authors note that prior to the onset of their ovarian cancer screening trial, 29.7% of 35 cancers diagnosed in the department were Stage I while after the trial was initiated, 58.8% of 85 ovarian cancers treated were Stage I.¹⁰ However, in such studies, lack of a control group raises the possibility of a "healthy-volunteer effect". It is also important to note that the "ovarian cancers" detected by screening in the Japanese trial included granulosa cell and borderline epithelial tumours. Mortality is unlikely to be reduced significantly by screen detection of these tumours, which have a good prognosis.

8.3 Precursor lesions

A central principle of cancer screening is detection of a pre-invasive or early invasive cancer, thereby reducing disease mortality and treatment morbidity. Many solid cancers have a pre-invasive or intra-epithelial phase. The cervical cancer model best represents this. About 30% of cervical high grade intraepithelial lesions may progress to invasive disease if left untreated.¹¹ Other cancers associated with detectable premalignant conditions include oesophagus, large bowel, endometrium, and vulva.

However, little is known about the natural history of ovarian cancer. The current view is that an unknown but probably predominant proportion of tumours arises de novo from the surface epithelium of the ovary or its inclusion cysts in the peripheral ovarian cortex¹². Pathologists who have identified dysplasia in the surface epithelium of the ovary or its inclusion cysts^{13 14} and who have studied the relation of benign (and borderline) epithelial lesions to carcinomas within the same specimen¹⁵ have presented persuasive evidence that benign and borderline lesions and dysplasia are precancerous in some cases. The frequency and speed of their evolution into cancer remain unknown. It is likely that they represent the minority of ovarian cancers.

The hallmark of preinvasive lesions in other epithelial cancers is the presence of an intraepithelial lesion with the histological features of cancer

but the absence of destructive stromal invasion. Borderline ovarian tumours, otherwise called ovarian neoplasms of low malignant potential or ovarian intraepithelial neoplasms, fulfil the histological criteria of preinvasive lesions. However, there is increasing evidence that suggests that borderline tumours are different from ovarian cancers. Although they can occasionally be multifocal at presentation, in a manner suggestive of metastatic disease, recent studies have shown that while, the majority of metastatic invasive ovarian cancers are in fact clonal in nature, metastatic borderline tumours, are truly multifocal and not from the same clone.¹⁶ In addition, borderline and invasive ovarian cancers do not share similar genetic events. The tumour suppressor gene *tp53* is mutated in ovarian cancers in up to 75% of cases while it is rarely mutated in borderline tumours. *K-ras* mutations occur relatively frequently in borderline tumours and uncommonly in ovarian cancers, the exception being mucinous cystadenocarcinoma.¹⁷⁻¹⁹ Borderline tumours are rarely aneuploid whilst cancer is typically so.²⁰ So, although borderline tumours resemble intraepithelial neoplastic lesions, they are probably not the major precursor lesion for the majority of invasive ovarian cancers. Borderline tumours however, contribute to increase the surgical intervention rate in screening strategies, as they are phenotypically similar to ovarian cancers, making it almost impossible on imaging to differentiate the two.

The other possible precursor lesions for invasive ovarian cancer are benign ovarian neoplasms. If a large proportion of ovarian cancers arose in this way, removal of benign cysts in a screening programme would impact on

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future ovarian cancer incidence. Crayford et al analysed data from a cohort of 5479 self-referred, asymptomatic women who participated in ovarian cancer screening trial and had been followed up for an average of 15 years. 202 women had bilateral salpingo-oophorectomies as a result of findings on ultrasound screening. The removal of persistent ovarian cysts was not associated with a decrease in the proportion of expected deaths from ovarian cancer. The main limitations of this study were the use of ovarian cancer mortality rather than incidence as the end point, the absence of a control group and the fact that 59% of the lesions removed were physiological or simple cysts rather than benign neoplasms.²¹ More recently, Hartge et al ²² assessed whether asymptomatic complex ovarian cysts detected on ultrasonography in postmenopausal women were precursors to ovarian cancer. In 20,000 postmenopausal women enrolled in an ongoing randomised cancer screening trial, they compared the risk factor profile of women with complex ovarian cysts to the established risk factors for ovarian cancer. The women with complex ovarian cysts did not share the same risk factor profile as ovarian cancer, suggesting that majority of the complex cysts and other clinically suspicious abnormalities detected on ultrasonography were not immediate precursors of ovarian cancer.

Thus, a true precursor lesion for ovarian cancer has yet to be identified, limiting the goal of screening to detection of asymptomatic, preclinical low volume disease.

8.4 Target populations

There are two groups of women who are at risk of ovarian cancer.

8.4.1 High risk population

Hereditary syndromes account for approximately 5% of ovarian cancers. First-degree female relatives of affected members from ovarian cancer only or breast and ovarian cancer or hereditary non-polyposis colon (HNPCC) cancer families have a lifetime risk of developing ovarian cancer of 10% or more. Much of this risk in nonHNPCC families is due to mutations in the BRCA1 and BRCA2 genes. The average cumulative risks by age 70 years for ovarian cancer was 39% (18%-54%) in BRCA1-mutation carriers and 11% (2.4%-19%) in BRCA2 mutation carriers.²³ In HNPCC there is a 7-12% lifetime risk of ovarian cancer.²⁴ In such populations, the ovarian cancers occur somewhat earlier with the median age at diagnosis of ovarian cancer in BRCA1 carriers being 51 years and in BRCA2 carriers 57 years. In such high risk populations, the most effective method of risk reduction is risk reducing bilateral salpingo-oophorectomy when women have completed their families and are in their forties.^{15 25-29} In those unwilling to undergo surgery, screening is an option, although the efficacy of such surveillance is not yet established.³⁰

8.4.2 General population

90% of ovarian cancers are sporadic and occur in the general population,. Age is a strong determinant of risk with over 90% of cases occurring in women aged over 45¹. Age specific rates peak in the ages of 74-85 (Figure 8-3).² The age adjusted rate for ovarian cancer in women over the age of 50 based upon 1996-2000 US cancer registry data was 44.97 (95%CI 44.01 - 45.95) per 100,000 while that in women below the age of 50 was 6.16 (95%CI 5.94 – 6.39).³¹ General population screening trials are usually limited to women over 50 years of age.

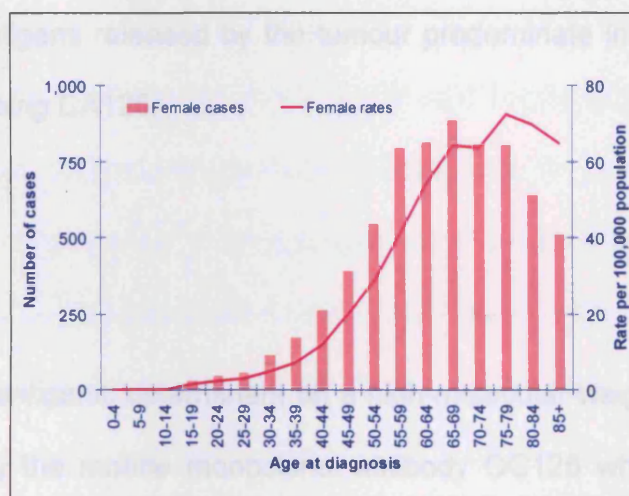


Figure 8-3: Numbers of new OC cases and age specific incidence rates, UK 2003²

Other risk factors for targeting women at increased risk within the general population are menopausal status, years of oral contraceptive use and parity. Various groups are investigating the role of single nucleotide polymorphisms in low and moderate penetrance genes and their

interactions with environmental and lifestyle factors. It may be possible in the future to identify women with increased susceptibility for sporadic ovarian cancer based on their genetic profile and lifestyle factors.

8.5 Screening tests

A variety of screening tests based on biochemical, morphological, vascular and cytological tumour markers have all been explored with varying success.

8.5.1 Tumour markers

Circulating antigens released by the tumour predominate in this group, the best known being CA125.

CA125

CA125 is an antigenic determinant on a high-molecular-weight glycoprotein recognised by the murine monoclonal antibody OC125 which was raised using an ovarian cancer cell line as an immunogen.³² It is expressed by amnion and coelomic epithelium during foetal development. In the adult, it is found in structures derived from coelomic epithelium (the mesothelial cells of the pleura, pericardium, and peritoneum) and in tubal, endometrial and endocervical epithelium. Curiously, the surface epithelium of normal foetal and adult ovaries do not express the determinant, except in inclusion cysts, areas of metaplasia and papillary excrescence.³³ More recently expression

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has been identified outside the female genital tract in epithelial cells of the lung, breast, conjunctiva and glandular epithelium of the prostate gland.³⁴

Although CA125 antigen was first detected in 1981, very little is known about its biochemistry and genetics. In the late 1990s, molecular analysis of the CA125 antigen identified a mucin-type glycoprotein which is highly glycosylated with the protein moiety rich in serine, threonine and praline.³⁵ Possibly because of the mucinous nature of CA125 its peptide moiety has been very difficult to clone. In 2001, molecular cloning of the CA125 ovarian cancer antigen led to the identification of a new mucin, MUC16.^{36 37} The gene has been localized provisionally to chromosome 19 p13.3.

The CA125 antigen carries two major antigenic domains classified as A, the domain binding monoclonal antibody OC125 and B, a domain binding monoclonal antibody M11³⁸. Immunoassays for measuring serum CA125 levels are now usually based on a heterologous assay (CA125II) using both monoclonal antibodies (M11 and OC125), as opposed to the original homologous assay done with monoclonal antibody OC125 alone. The CA125II assay is sensitive and reliable for measuring serum CA125, and fully retains the cut-off values of 35 and 65 units/ml that were defined with the original CA125 immunoradiometric assay.³⁹ The serum value of 35U/ml, representing 1% of healthy female donors, is widely accepted as the upper limit of normal.⁴⁰ It should be noted that this is an arbitrary cut off which may not be ideal for some applications of CA125. For example in postmenopausal women or in patients after hysterectomy CA125 levels tend

to be lower than in the general population and lower cut-offs may be more appropriate; 20U/ml and 26U/ml have been suggested.^{41 42}

Approximately 83% of patients with epithelial ovarian cancer will have CA125 levels >35U/ml.^{40 43} 50% of patients with Stage I disease have elevated levels while raised levels are found in >90% of women with more advanced disease.⁴⁴ Lower incidences of CA125 elevation are found in mucinous, clear cell and borderline tumours⁴⁵⁻⁴⁷. Elevation of serum CA125 may also be associated with other malignancies (pancreas, breast, colon, bladder, liver, lung)⁴⁸ as well as benign disease (diverticulitis, uterine fibroids, endometriosis, benign ovarian cysts, tubo-ovarian abscess, hyperstimulation syndrome, ectopic pregnancy)⁴⁹ and physiological conditions (pregnancy and menstruation).⁵⁰ Many of these non-malignant conditions are not found in post-menopausal women, thereby improving the diagnostic accuracy of an elevated level in this population.

Various refinements in the last decade have lead to improvements in sensitivity and specificity of ovarian cancer screening using CA125. Key among them are:

(1) Pelvic ultrasound as a second line test

Specificity of screening with CA125 was initially improved by the addition of pelvic ultrasound as a second line test to assess ovarian volume and morphology. Using multimodal screening incorporating sequential CA125 and pelvic ultrasound, a specificity of 99.9% and positive predictive value of

26.8% (approximately 4 operations for each cancer) for detection of ovarian and fallopian tube cancer was achieved in 22,000 postmenopausal women^{51 52}. With the accumulation and analysis of data (as part of the work undertaken in this thesis), ovarian morphology has been used to refine algorithms for the interpretation of ultrasound in postmenopausal women with elevated CA125 levels^{53 54}.

(2) Risk of Ovarian Cancer Algorithm (ROCA) to interpret CA125 results

The CA125 based screening strategy was further improved by incorporating a more individualised approach rather than absolute cut-off levels to interpret CA125 results. Detailed analysis of over 50,00 serum CA125 values involving 22,000 volunteers followed up for a median of 8.6 years in the study by Jacobs et al revealed^{8 51} that elevated CA125 levels in women without ovarian cancer are static or decrease with time while levels associated with malignancy tend to rise. This finding has been incorporated into a computerised algorithm that uses an individual's age specific incidence of ovarian cancer and serial CA125 profile to estimate her risk of ovarian cancer (ROC)^{55 56}. The closer the CA125 profile to the CA125 behaviour of known cases of ovarian cancer, the greater the risk of ovarian cancer. The final result is presented as the individual's estimated risk of having ovarian cancer so that a ROC of 2% implies a risk of 1 in 50. The ROC algorithm increases the sensitivity of CA125 compared to a single cut-off value because women with normal but rising values are identified as being at increased risk. At the same time, specificity is improved as women

with static but elevated levels are classified as low risk. For a target specificity of 98%, the ROC calculation achieved a sensitivity of 86% for preclinical detection of ovarian cancer.⁵⁵ This approach forms part of the multimodal screening strategy in the recently completed pilot randomised control trial of ovarian cancer screening at Bart's London⁵⁷ and is part of the ongoing UK Collaborative Trial of Ovarian Cancer Screening (www.ukctocs.org.uk). The ROC algorithm is also being evaluated prospectively as part of the OCS strategy in two trials in 'high risk' women in USA – one under the auspices of the Cancer Genetics Network and the other by the Gynaecology Oncology Group (GOG199 study protocol). In the UK, it is to be used in Phase II of the UK Familial Ovarian Cancer Screening Study (UKFOCSS).

New tumour markers

Certain tumours (e.g. mucinous and borderline carcinomas) are less likely to be associated with elevated CA125 levels than invasive serous cancers.⁴⁴ In the past decade, significant progress has been made in developing novel tumour markers for use in OCS. While some like CA72-4 or TAG 72^{47 58-60}, OVX1⁶¹⁻⁶³ and LPA⁶⁴ have not lived up to their initial promise. Novel markers undergoing current evaluation are listed in Table 8-1.⁶⁵ It is important to appreciate that most of these have been so far studied using samples from women with clinically diagnosed ovarian cancer (i.e. differential diagnosis of ovarian cancer) as opposed to asymptomatic women with pre-clinical disease (i.e. early detection of ovarian cancer). They

therefore need to undergo significant further evaluation before their potential in OCS can be determined.

In the new era of proteomics, in addition to individual markers, there has been a great deal of interest in identifying global patterns of serum proteins and peptides that relate to cancer risk. A wide range of techniques are now available for protein identification and characterization where high sensitivity and specificity is combined with high throughput. Surface-Enhanced Laser Desorption Ionization Time-Of-Flight (SELDI-TOF) analysis and Matrix-Associated Laser Desorption Ionization Time-Of-Flight (MALDI-TOF) technology have the potential to identify patterns or changes in thousands of small proteins (<20 kd). When combined with matrices that selectively absorb certain serum proteins, these approaches can globally analyze almost all small proteins in complex solutions, such as serum or plasma.^{66 67} Combination of mass spectra generated by these new technologies and artificial-intelligence-based bioinformatics algorithms have been used to discover small sets of key protein values that discriminate normal from ovarian cancer patients. A preliminary study reported that using SELDI-TOF to analyze the proteomic spectra patterns of serum, a discriminatory pattern correctly identified all 50 ovarian cancer cases in the masked set including all 18 stage I cases with a specificity of 95% (87--99), and positive predictive value of 94%⁶⁸. The results of this study have not so far been validated and the limitations of the study design and data analysis have been discussed in some detail in the literature.⁶⁹⁻⁷⁵ While there are challenging issues related to sample processing, study design as well as the reproducibility,

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sensitivity, and specificity of this new technology, the implications of such proteomic spectrum analysis for the identification of novel tumour markers is huge..⁷⁶ It is possible that in the future, the early detection of ovarian (and other) cancers will involve high throughput proteomic profiling either alone or in combination with markers already in use.

Table 8-1: Tumour markers currently undergoing evaluation for OCS

Tumour marker	Description
M-CSF	Serum macrophage colony-stimulating factor is a cytokine produced constitutively by normal as well as neoplastic ovarian epithelium. Levels are elevated in 68% of patients with ovarian cancer compared to 2.5% of apparently, healthy controls ⁷⁷ . Elevated levels have been found in ovarian cancer patients with normal levels of CA125 ⁷⁷ . While CA 125 alone was elevated in 67% of 46 patients with stage I ovarian cancer, CA125 or M-CSF was elevated in 91% ⁷⁸ .
Prostasin	Prostasin is a serine protease normally secreted by the prostate gland. It was identified as a biomarker following identification of gene over-expression using micro array technology on RNA pooled from OC and normal human ovarian surface epithelial cell lines. The combination of CA 125 and prostasin in 37 patients with non-mucinous ovarian cancer and 100 control subjects, resulted in a sensitivity of 92% (95% CI = 78.1% to 98.3%) and a specificity of 94% (95% CI = 87.4% to 97.7%) for detection of ovarian cancer ⁷⁹ .
Osteopontin	Osteopontin is another bio-marker that has been identified by exploiting gene expression profiling techniques. Plasma levels of osteopontin were significantly higher in patients with EOC compared with healthy controls, patients with benign ovarian disease and with other gynaecologic cancers. ⁸⁰ However, Stage IV OC patients and those with ascites had higher plasma osteopontin levels than those without ascites and with early stage disease. The sensitivity in detecting OC was 81.3% compared to 84.4% with CA125 alone and specificity was moderate. Sensitivity increased to 93.8% when the markers were combined. ⁸¹ In urine samples from OC patients, urinary osteopontin fragments have been described. ⁸²

Table 8-1: Tumour markers currently undergoing evaluation for OCS (contd)

Kallikreins	The human kallikrein gene family currently consists of 15 members which includes prostate-specific antigen (hK3). Preliminary reports indicate that two kallikreins (hK6, hK5 and hK10) may be useful serum biomarkers for diagnosis of ovarian ⁸³⁻⁸⁵ .
HE4	Among the genes most commonly identified in gene expression profiles of epithelial ovarian carcinomas (EOC) is the gene for human epididymis protein 4 (HE4). ⁸⁶ On immunohistochemical assessment, normal ovarian surface does not express HE4, while cortical inclusion cysts lined by metaplastic Mullerian epithelium abundantly express the protein. Its expression in tumours is restricted to certain histological subtypes: 93% of serous and 100% of endometrioid EOCs expressed HE4, whereas only 50% and 0% of clear cell carcinomas and mucinous tumours, respectively, were positive. ⁸⁷ Although the function of the HE4 protein is unknown, it is a member of a family of stable 4-disulfide core proteins that are secreted at high levels. In a blinded study on sera from postmenopausal patients with ovarian carcinoma and controls, the specificity and sensitivity of the HE4-based ELISA was found to be equivalent to that of the CA125 assay. However, the HE4 assay may have an advantage over the CA125 assay in that it is less frequently positive in patients with non-malignant disease. ⁸⁸
Mesothelin	Mesothelin is a cell surface glycoprotein that is present on normal mesothelial cells and over expressed in several cancers including ovarian tumours. ⁸⁹ Using a sandwich ELISA developed in the laboratory, the level of circulating antigen was found to be significantly elevated in sera from patients with ovarian carcinoma, as compared with healthy controls and patients with other tumours. ^{90 91} One of the current focuses is to use mesothelin as a target for immune-based therapies.

Table 8-1: Tumour markers currently undergoing evaluation for OCS (contd)

Soluble EGF receptor	EGF receptor (ErbB1) over expression is common in human OC-derived cell lines and tumours. Recently, an immunosorbent assay that detects an approximately 110-kDa soluble analogue of EGF receptor (sEGFR) has been described. Serum sEGFR concentrations in stage I/II and stage III/IV EOC patients have been found to be significantly lower than in healthy women. Logistic regression models showed that lower serum sEGFR concentrations are associated significantly with a greater risk of EOC and age or menopausal status-specific cut-off values for sEGFR concentration are appropriate. By maintaining a test specificity of approximately 95% across the strata of age or menopausal status with appropriate cut-off values, sEGFR concentrations had a sensitivity for detecting stage I/II of 64-67% and stage III/IV of 75-81%) in young, premenopausal women. ^{92 93}
Inhibin	Serum inhibin is an ovarian product, which decreases to non-detectable levels after menopause. However, certain ovarian cancers (mucinous carcinomas and sex cord stromal tumours such as granulosa cell tumours) continue to produce inhibin, which provides a basis for a serum diagnostic test. Available data show that inhibin assays which detect all inhibin forms, i.e. assays which detect the alpha subunit both as the free form and as an alphabeta subunit dimer provide the highest sensitivity/specificity characteristics as an ovarian cancer diagnostic test ⁹⁴

Use of marker panels

Use of multiple markers may increase the sensitivity for early detection of ovarian cancer. However, increased sensitivity is usually associated with decreased specificity. A panel of 8 different markers (CA 125, M-CSF, OVX1, LASA, CA15-3, CA72-4, CA19-9, CA54/61) improved the sensitivity for discriminating malignant from benign pelvic masses⁹⁵. Using the same data set, a subset of four markers (serum CA-125II, CA 15-3, CA 72-4, and M-CSF) analysed using an artificial neural network demonstrated improved sensitivity over CA125 alone (87.5% versus 68.4%) while maintaining comparable specificity. Estimates from the training set were applied to an independent validation set of 60 stage I to II OC patients and 98 healthy controls from two other centres. Combining information on CA-125II, CA 72-4, and M-CSF significantly increased preoperative early-stage sensitivity from 45% with CA-125II alone to 70%, while maintaining 98% first-line specificity. In addition, greater specificity using multiple markers might be attained if serial values are employed.⁹⁶ Preliminary data on a panel of five serum tumour markers (CA125, HER-2/neu, urinary gonadotropin peptide, lipid-associated sialic acid, and Dianon marker 70/K) obtained during 6 years of follow-up of 1257 healthy women at high risk of ovarian cancer suggests that, individual-specific screening rules may be developed with the potential to improve early detection of ovarian cancer.⁹⁷

8.5.2 Imaging

Real time ultrasound screening is used in an attempt to detect the earliest possible architectural changes in the ovary that accompany carcinogenesis. Transvaginal ultrasound (TVS) is preferred because of the more detailed images obtained. Both ovarian volume and morphology are assessed with cut-offs for volume ranging from 8mls to 20mls depending on menopausal status.⁹⁸⁻¹⁰⁰ The lack of physiological changes in ovarian volume in postmenopausal women helps decrease the number of false positives when compared to premenopausal women. However even in older women there is a high prevalence of benign ovarian lesions. In an ultrasound and histopathological autopsy study of 52 consecutive postmenopausal women, (mean age 79, range 64-96 years), who died from causes other than gynaecological or intraperitoneal cancer, 56% were found to have a ≤ 50 mm benign adnexal lesion.¹⁰¹ In a more recent autopsy study of 234 postmenopausal women who had died from non-gynaecological diseases ovarian cysts were found in 15.4%. All cysts were benign, except for one woman, who had bilateral borderline serous cystadenoma.¹⁰² Ultrasonography can therefore lead to the detection of many benign ovarian tumours and hence unnecessary surgery in healthy, asymptomatic women.

Other issues with ultrasound screening for adnexal masses is the lack of standard definitions and classification.¹⁰³ The International Ovarian Tumor Analysis (IOTA) group have attempted to provide standardised terms and procedures to describe anatomical features by B mode imaging. They have provided definitions for morphological features such as septum, solid areas, papillary projections, cyst wall irregularity. All lesions have been divided

qualitatively into a total of six categories that include unilocular, unilocular-solid, multilocular, multilocular-solid, solid and non-classifiable tumours.¹⁰⁴

An additional issue is subjective assessment of images which leads to significant inter observer variability. In a prospective study of 300 patients whose pre-operative recorded images were independently reviewed by 5 ultrasonographers with different qualifications and degree of experience, the most experienced investigator obtained an accuracy of 92% while less experienced observers obtained significantly lower accuracy (between 82% and 87)¹⁰⁵. Another prospective study based on 173 women who were also scanned preoperatively showed that with experienced sonographers, subjective evaluation of the gray-scale ultrasound image is the most accurate method for distinguishing between benign and malignant adnexal lesions.¹⁰⁶ Self-teaching computer models such as neural networks that may increase the reproducibility of results are being investigated in order to address the problem of the subjectivity of ultrasound.¹⁰⁷

Given the high incidence of benign adnexal lesions, it is crucial to be able to characterise ovarian cysts detected on scanning in order to reduce false positive rates. As data regarding outcome accumulates with long-term follow up of the participants of the early screening trials, it has been possible to correlate the risk of ovarian cancer with various ultrasound findings. The work done in the initial chapters of this thesis established that use of complex ovarian morphology to interpret pelvic ultrasound increases the sensitivity and positive predictive value in multimodal screening.⁵⁴ Similarly

follow up of participants in the Kentucky ultrasound based OCS trial established that unilocular ovarian cysts <10cm in diameter are found in 18% of asymptomatic postmenopausal women aged over 50 years and are associated with an extremely low risk of malignancy.¹⁰⁸⁻¹¹⁰ In cysts with a mean diameter of >5 cm, however, there is a chance that papillary formations or solid parts may be missed by TVS.¹¹¹ Hence conservative management is often limited to smaller cysts. In contrast to unilocular or simple cysts, complex ovarian cysts with wall abnormalities or solid areas are associated with a significant risk for malignancy.¹⁰⁹ Based on gross anatomic changes at the time of surgery, papillary projections have the highest and simple cysts and septal thickness the lowest correlation with a diagnosis of ovarian malignancy.¹¹² Numerous weighted morphological indices based on ovarian volume, outline, presence of papillary projections and cyst complexity (i.e. number of locules, wall structure, thickness of septae and echogenicity of fluid) have been proposed to improve discrimination of benign and malignant masses . There is no standardised index as yet with systems varying on the number and type of variables evaluated.¹¹³⁻¹¹⁶ On prospective testing none of the current models have been found to beat an expert sonologist.^{117 118} Further refinement of mathematical models and review of results of multicentre trials are need before clinical use of these mathematical models can be advocated.

In the recently reported prospective clinical study by the IOTA group involving nine European ultrasound centres, 1,066 symptomatic women with an adnexal mass underwent TVS gray scale and colour Doppler ultrasound

examination by a skilled examiner before surgery. A standardized examination technique and predefined definitions of ultrasound characteristics were used. The 1,066 masses included 55 ovarian borderline tumours, 144 primary invasive epithelial ovarian cancers (42 stage I, 102 stages 2-4), 25 rare malignancies, and 42 metastatic tumours. Most (56%) metastatic tumours and most (60%) rare types of tumour were solid and richly vascularised at colour Doppler ultrasound examination. Borderline ovarian tumours and stage I primary invasive EOC differed significantly from stages II-IV primary invasive EOC in that they were larger (median volume 375 ml and 695 ml vs. 209 ml), more frequently had papillary projections (64% and 67% vs. 41%), were multiloculated without solid components (18% and 14% vs. 2%) and less often purely solid (5% and 7% vs. 38%). With increasing degree of invasiveness, ascites became more common and the proportion of solid tissue increased.¹¹⁹ Diagnostic difficulties were particularly related to borderline tumours, papillary cystadenomas, struma ovarii and some myomas. Logistic regression models did not seem to solve the diagnostic problem in difficult pelvic masses.¹²⁰ Similar data on large numbers of adnexal masses detected by screening asymptomatic healthy women is not yet available.

One of the main strategies to decrease false positives in TVS screening is repeat scanning 4-6 weeks following initial detection to check for persistence or change in the morphology or size of the detected abnormality.^{100 108} Among postmenopausal women in the Kentucky ultrasound screening trial, 49% of unilocular cysts and 55% of complex tumours resolved

spontaneously within 60 days of the initial scan.¹⁰⁸ In the ultrasound based European Randomised Control Trial Of Ovarian Cancer Screening (which recruited about 15,000 postmenopausal women before it was discontinued), multicystic and multilocular cysts in addition to unilocular cysts were managed conservatively if the morphology remained unchanged on repeat scanning.¹²¹ This parallels the move in clinical practice of conservative management of adnexal cysts judged to be benign at transvaginal ultrasound examination when they are incidentally detected in postmenopausal women.¹¹⁷ Follow up data on such women will be important in refining optimal strategies for operative intervention in screening.

Neovascularisation is an obligate early event in tumour growth and neoplasia. Fast growing tumours contain many new vessels which have less smooth muscle in their walls and therefore provide less resistance to blood flow when compared to vessels within benign ovarian tumours. Colour-flow Doppler imaging uses these altered blood flow patterns as markers to differentiate malignant from physiologic and benign lesions. However while it has been demonstrated that the mean PI of vessels supplying ovarian cancers is lower than that of vessels supplying benign ovarian tumors, the overlap in vascular resistance between these two groups prevents reliable separation of malignant from benign ovarian tumors. The optimal parameters and cut-off levels (pulsatility index (PI) <1.0, resistance index <0.4 or 0.6, or peak flow velocity) with the highest predictive value for malignancy have been difficult to define. The IOTA group have attempted to provide standardized terms and procedures to describe the vascular

features detected by colour flow Doppler imaging. The vascular features are assessed by examination of the entire tumour by colour flow Doppler imaging. Scores of 1 to 4 are given dependent on the degree of blood flow visualized, score of 1 being absence of blood flow and 4 being highly vascular lesion with marked blood flow and 2 and 3 are in between.¹⁰⁴

Colour Doppler has been used both as a first line screening test in combination with transvaginal ultrasound^{122 123} as well as a second line test^{121 124} in screening both general and high risk populations. The initial promise of Doppler to differentiate between malignant and benign ovarian masses and therefore improve the specificity of ultrasound^{122 123} has not been sustained.¹²⁵ It was initially reported that lack of blood flow in an ovarian tumor as detected by color Doppler could preclude cancer. This has not been substantiated by data from either clinical studies¹¹⁶ or screening trials. In the Kentucky ultrasound screening trial, 6% of ovarian tumors without blood flow were malignant. Even when Doppler examinations were simplified and limited to the expression of internal color flow, gray-scale sonography was a more sensitive indicator of malignancy than Doppler sonography.^{106 116} Key issues with regard to Doppler examination as a possible second-line study for ultrasound-based ovarian cancer screening protocols are whether the examination should focus on quantitative or qualitative differences in blood flow within complex masses, difficulties with interobserver variation and lack of standardisation. At present the consensus of opinion is that colour flow Doppler evaluation of ovarian

masses will not significantly improve the accuracy of gray-scale sonography except perhaps in a few highly selected cases.

Three-dimensional (3D) power Doppler ultrasound provides a new tool to evaluate features of tumor vascularity. Combined evaluations of morphology and neovascularity using 3D ultrasound, 3D power Doppler and contrast-enhanced 3D power Doppler helps delineate overall vessel density and branching patterns within an intratumoral abnormality. Preliminary studies on symptomatic patients suggest increased accuracy in differentiating benign from malignant adnexal lesions.¹²⁶⁻¹³⁰ In a prospective study of 656 consecutive women with adnexal masses scheduled for surgery in two European university centres, TVS had a false-positive rate of 18% while the false-positive rates of colour Doppler and power Doppler imaging were 4.6 and 7.4%, respectively. Although the overall diagnostic accuracy of the two techniques seemed comparable, colour Doppler imaging showed a higher false-negative rate.¹³¹ In the screening context, 3D ultrasonography with power Doppler has recently been used as a second line test in a TVS based OCS study of 3,201 asymptomatic women aged ≥ 50 years. Twenty-five patients with persistent abnormalities after primary and secondary screening underwent surgery and five Stage I EOC were detected. 3D ultrasonography and power Doppler were indicative of malignancy in all 5 patients whereas colour flow Doppler was negative in 2 of the patients with stage I disease.¹³²

Magnetic resonance imaging (MRI), computerised tomography (CT) and positron emission tomography (PET) have been used as third line tests to

improve discrimination between benign and malignant adnexal lesions in the ovarian arm of the Prostate Lung Colon Ovary Screening Trial (PLCO)¹³³. There are as yet no formal reports analysing their specific contribution in reducing surgical intervention rates. Clinical studies exploring the role of CT and MR imaging in the diagnosis of OC seem to suggest that where there is uncertainty on ultrasound assessment, MRI may provide more specific information and help to better distinguish benign from malignant.¹³⁴ Accuracy is particularly high with regard to mature cystic teratomas, endometriotic cysts, and leiomyomas. CT however is not useful for differential diagnosis of adnexal masses because of poor soft tissue discrimination, except for fatty tissue and calcification.¹³⁵⁻¹³⁸ However, it is to be noted that negative MRI or PET results do not rule out early-stage ovarian cancer or borderline malignancies.¹³⁹

The tumour marker serum CA125 is frequently used to assess the malignant potential of a persistent adnexal mass detected on ultrasound screening.¹³³¹⁴⁰ The Risk of Malignancy Index (RMI) which incorporates the CA125 value and an ultrasound scoring system and menopausal status is often used in the clinical context to triage management in women with suspicious adnexal masses.¹⁴¹⁻¹⁴⁶ However, it is crucial to note that most screening trials do report EOC that were detected on ultrasound but had normal CA125 levels.^{132 133 147}

8.6 Screening Strategies

The main screening tests, serum CA125 and TVS have been incorporated into three distinct screening strategies:

- (1) Multimodal based on measurement of the serum tumour marker CA125 as the first line test with TVS if the level is abnormal. Increasingly the serum CA125 is interpreted using the Risk of Ovarian Cancer (ROC) algorithm
- (2) Ultrasound based on primary screening using TVS followed by a repeat scan in 6-8 weeks if the first detects an abnormality
- (3) Combined where both serum CA125 and TVS are done as first line tests.

Currently the first two strategies are being investigated in UKCTOCS which is the subject of part of this thesis and the third strategy has been adopted in the ovarian arm of the PLCO trial and in many of the reported 'high risk' screening studies.

8.7 Screening interval

Most general population trials to date have empirically chosen annual screening. If the screening interval is too short, this will lead to higher false positive rates with its resultant cost and morbidity. If however the screening interval is too long then one may miss the opportunity of detecting women with early stage disease. Based on an analysis of follow up data from the Bart's trial of 22,000, Skates et al estimated the preclinical phase of the disease in the general population to be about 1.9 years.⁵⁰ The large serum banks with serial blood samples resulting from all the trials will help establish

lead time for OC with some degree of accuracy. In the high-risk population, studies are underway which use much smaller screening intervals of 3-4 months. It is however likely that familial OC in the younger high-risk patients is a somewhat different disease from the sporadic disease.

8.8 Completed trials in the general population

Numerous trials have been completed and reported in the general population. They are detailed in Table 8-2 and Table 8-3. This includes the prevalence screen of the pilot RCT reported in section 11 of this thesis. The only large general population study not included in the table is the recently reported OC prevalence screen in the PLCO trial (Figure 8-4). In this trial a combined strategy using both serum CA125 and ultrasound as first line tests was adopted for the first three years of screening. Of 39,115 women randomised to receive screening, 28,816 received at least 1 test. Abnormal TVS was found in 1338 (4.7%), and abnormal CA-125 in 402 (1.4%). Twenty-nine neoplasms were identified (26 ovarian, 2 fallopian, and 1 primary peritoneal neoplasm). Nine were tumors of low malignant potential and 20 were primary invasive.¹³³ The positive predictive value for invasive EOC was 3.7% for CA125, 1.0% for TVS, and 23.5% if both tests were abnormal. This equals 41.2 operations per invasive EOC detected if TVS alone as used versus 4.1 if serum CA125 alone was used as a first line test. The data confirms the findings of the large prospective studies of OCS in the general population listed in Table 8-2 and Table 8-3. Sequential multimodal screening with serum CA125 as the first line test has superior

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specificity and leads to about 4-5 operations per case of invasive EOC detected when compared to strategies based on TVS alone which result in 20-40 operations per case detected.

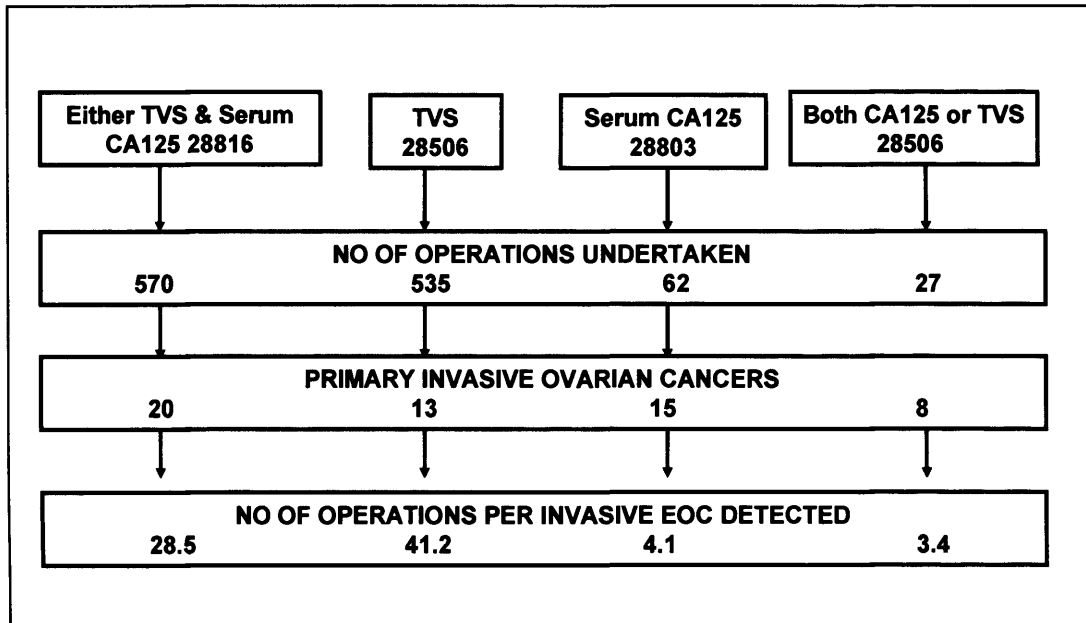


Figure 8-4: Prevalence screen in the ovarian arm of the PLCO trial

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Table 8-2: Prospective OCS studies in the general population using the multimodal strategy

Authors	Main features	Screening strategy	No. screened	No. of Primary EOC detected () ^a	No. of invasive positive screens	No. of operations EOC detected
SERUM CA125 ALONE						
Einhorn et al 1992	Age ≥40 years	Serum CA125	5550	6 2 stage I	175 ^a	29 ^b
MULTIMODAL APPROACH - CA125 (LEVEL 1 SCREEN), then USS (LEVEL II SCREEN)⁶⁶						
Menon et al 2005 ⁵⁷	Age ≥50 years Postmenopausal RCT	Serum CA125 interpreted using ROC	6532	3 2 Stage I (1) ^a	16	5.3
Jacobs et al 1999	Age ≥45 years (median 56) Postmenopausal RCT	TAS/TVS, if CA125↑ 3 screens	10958	6 3 stage I	29	4.8
Jacobs et al 1988, 1993, 1996 ^{51 52 148}	Age ≥45 years (median 56) Postmenopausal	Serum CA125 TAS, if CA125↑	22000	11 4 stage I	41	3.7
Adonakis et al 1996	Age ≥45 years (mean 58)	Serum CA125 TVS, if CA125↑	2000	1 1 stage I (1) ^a	15	15
Grover et al 1995	Age ≥40 years (median 51) or with family history (3%)	Serum CA125 TAS/TVS, if CA125↑	2550	1 0 stage I	16	16
TOTAL			44040	22 (2)^a	117	5.3

RCT = randomised controlled trial; TAS = transabdominal ultrasound; TVS = transvaginal ultrasound; ROC= risk of ovarian cancer. ^a Borderline/granulosa tumours detected are shown in parenthesis; ^b Not all of these women underwent surgical investigation as the study design involved intensive surveillance rather than surgical intervention

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Table 8-3: Prospective OCS studies in the general population using ultrasound as the primary test

Authors	Subjects	Screening strategy	No. screened	No. of primary invasive EOC detected () ^a	No of positive screens	No of positive screens/ EOC detected
USS ONLY APPROACH -USS (LEVEL 1 SCREEN), then repeat USS (LEVEL II SCREEN)						
van Nagell et al 1995, ¹⁴⁹ 2000 ²⁶⁹ De Priest et al 1997, ¹⁴⁷ 2003 ¹⁵⁰	Age ≥ 50 years and postmenopausal OR >30 with family history	TVS Annual screens Mean 4 screens / woman	14,469	11 5 Stage I (6) ^a	180	16.3
Sato S et al 2000 ¹⁰	Part of general screening programme	TVS	51,550	22 17 Stage I	324	14.7
Hayashi et al 1999 ¹⁵¹	Age ≥ 50 years	TVS	23,451	3 0 Stage I (3) ^a	258	^b
Tabor et al 1994 ¹⁵²	Aged 46-65 years	TVS	435	0	9	-
Campbell et al 1989 ¹⁵³	Age ≥ 45 years (mean 53) or with family history (4%)	TAS 3 screens at 18 monthly intervals	5479	2 2 stage I (3) ^a	326	163
Millo et al 1989 ¹⁵⁴	Age ≥ 45 years OR postmenopausal (mean 54)	US (not specified)	500	0	11	-
Goswamy et al 1983 ¹⁵⁵	Age 39-78 Postmenopausal	TAS	1084	1 1 stage I		

TAS = transabdominal ultrasound; TVS = transvaginal ultrasound. ^a Borderline/granulosa tumours detected are shown in parenthesis. ^b Only 95 women consented to surgery and there are no follow up details on the remaining.

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Table 8-3: Prospective OCS studies in the general population using ultrasound as the primary test (contd.)

Authors	Subjects	Screening strategy	No. screened	No. of primary invasive EOC detected () ^a	No of positive screens	No of positive screens/ EOC detected
USS and CDI (LEVEL I SCREEN)						
Kurjak et al 1994 ¹²²	Aged 40-71 years (mean 45)	TVS and CDI	5013	4 4 stage I	38	9.5
Vuento et al 1995 ¹²³	Aged 56-61 years (mean 59)	TVS and CDI	1364	0 (1) ^a	5	-
USS (LEVEL 1) and other test (LEVEL II SCREEN)						
Kurjak et al 2005 ¹³²	Aged ≥50	TVS then 3D USS and power Doppler if TVS positive	3201	5 5 stage I	25	5
Parkes et al 1994 ¹²¹	Aged 50-64 RCT	TVS then CDI if TVS positive	2953	1 1 stage I	15 ^c	15
Holbert et al 1994 ¹⁵⁶	Postmenopausal, Aged 30-89 years	TVS then CA125 if TVS positive	478	1 1 stage I	33 ^d	33
Schincaglia et al 1994 ¹⁵⁷	Aged 50-69	TAS, then aspiration/ biopsy	3541	2 0 stage I	98	9.5
TOTAL (including studies on previous page)			113,518	52 (30)	1322	25.4

RCT = randomised controlled trial; TAS = transabdominal ultrasound; TVS = transvaginal ultrasound; CDI = colour Doppler

^a Borderline/granulosa tumours detected are shown in parenthesis

^c 86 women had abnormal USS prior to CDI.

^d Only 11 of these women underwent surgery.

With regard to apparent sensitivity for detection of ovarian cancer, very few trials have reported on follow up and interval (false negative) cancers. Published data is only available for prevalence screening in two of the multimodal trials (including the one detailed in chapter 8 of this thesis)^{52 57} and for both prevalence and incidence screening in the Kentucky trial⁹ (Table 8-4). In addition, in the PLCO trial, although no interval cancers have been reported in the year following the prevalence screen, some estimates of highest possible sensitivity can be derived for the multimodal and ultrasound strategy as both TVS and CA125 were used as first line tests. The apparent sensitivity at 1 year for both strategies seems to be in the range of 70-80%. Such conclusions are however very preliminary for given the numbers involved, confidence limits are wide.

The data with regard to detection of early stage cancers is extremely disappointing in the recent PLCO prevalence screen where all detected cancers were advanced. However in the previously reported studies detailed in Table 8-2 and Table 8-3, over 50% of the cancers detected were early stage with an ultrasound based strategy possibly offering greater sensitivity for early stage disease.

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Table 8-4: Apparent sensitivity for detection of primary invasive EOC in general population OCS trials

Authors	Screening strategy	Type of screen	Number of women	No. of primary invasive EOC detected	No of interval invasive EOC in one year from screen	Apparent sensitivity at one year for detection of EOC (%)
Multimodal strategy using CA125 as the first line test						
Menon et al 2005	CA125 interpreted using ROC algorithm	Prevalence	6532	3 2 Stage I	0	100
Jacobs et al 1996	CA125 interpreted using cut-off	Prevalence	22000	11 4 Stage I	3	78.6
Buys et al 2005	If serum CA125 with cut-offs was used as first line test	Prevalence	28803	15 0 Stage I	Not reported but in all 20 invasive EOC were detected using the combined strategy	75
Ultrasound strategy using TVS as the first line test						
Van Nagell et al 2003	USS using TVS	Both prevalence and incidence	7705 ^b	11 5 Stage I	3	78.6
Buys et al 2005	If TVS was used as first line test	Prevalence	28506	13 0 Stage I	Not reported but in all 20 invasive EOC were detected using the combined strategy	65

^b Restricted to the cohort of women aged ≥ 50 who were postmenopausal ^a A combined strategy using both serum CA125 and TVS was used

8.9 Current trials in the general population

With the screening strategies well defined and refined over the 1990s and the performance characteristics established, the next step was to establish if OCS did in fact save lives. Two large randomised controlled trials are now underway in the general population to assess the impact of screening on ovarian cancer mortality.

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial has completed enrolment of 78,000 women aged 55-74 at 10 screening centres in the U.S.A. with balanced randomization to intervention and control arms.¹⁵⁸ For ovarian cancer, women are screened using both CA125 and transvaginal ultrasound for three years and CA125 alone for a further two years. Follow-up will continue for at least 13 years from randomisation to assess health status and cause of death (Figure 8-5).

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) which is detailed in chapters 12, 13, 14 of this thesis has also completed recruitment of over 200,000 postmenopausal women who have been randomised to either control, screening with ultrasound or multimodal screening (www.ukctocs.org.uk). The primary end point is ovarian cancer mortality. The trial will also comprehensively address the issues of physical and psychological morbidity of screening, acceptability, and compliance of the target population and health

economics. There is a direct comparison of the two screening strategies. The trial is expected to report in 2012.

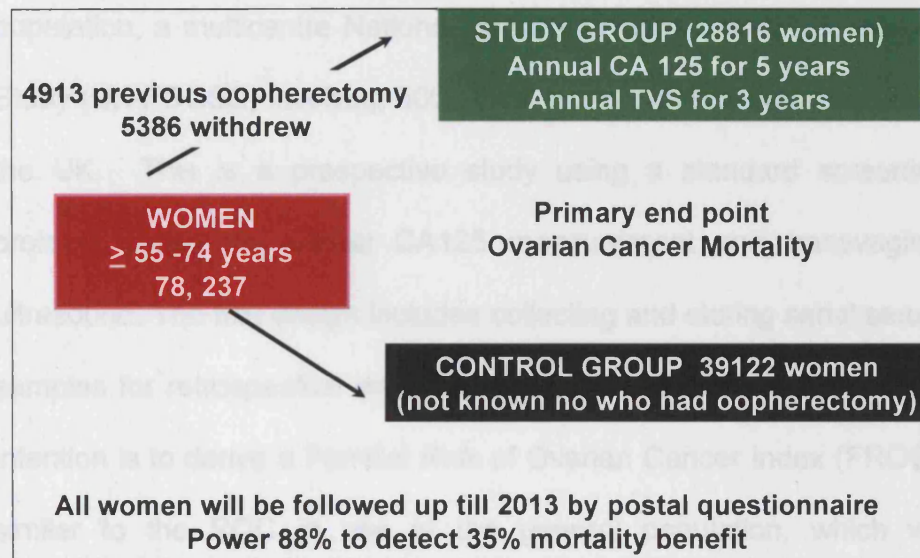


Figure 8-5: Design of the OCS arm of the Prostate Lung Colon Ovary trial

8.10 Trials in a high risk population

In women with strong evidence of a hereditary predisposition, screening is recommended although there is no conclusive evidence available that screening has an impact on ovarian cancer mortality. As a result, a randomised control trial of screening in this population is no longer feasible or ethical. Screening is problematic in this population as it includes premenopausal women who have a higher incidence of false positive CA125 elevations and ultrasound abnormalities. In addition, recent reports suggest that multifocal peritoneal serous

papillary carcinoma may be a phenotypic variant of familial ovarian cancer and may be difficult to detect using current screening tests.²¹

In order to develop an optimal screening strategy in the high risk population, a multicentre National Familial Ovarian Cancer Screening Study (UK-FOCSS) involving 5000 'high risk' women is being set up in the UK. This is a prospective study using a standard screening protocol based on annual CA125 measurement and transvaginal ultrasound. The trial design includes collecting and storing serial serum samples for retrospective analysis of CA125 and other markers. The intention is to derive a Familial Risk of Ovarian Cancer Index (FROC), similar to the ROC in use in the general population, which will incorporate in addition to the serial CA125 profile, data on family history and mutation analysis. A similar trial is underway in the USA under the auspices of the Cancer Genetics Network of the National Cancer Institute with the scope for meta-analysis in the future.

8.11 Conclusion

There are numerous answered questions and many aspects of ovarian cancer screening are still poorly understood, including whether or not there are precursor lesions, the rate of disease progression, and to what extent transvaginal ultrasonography and CA125 detect different cancers. There is also concern about the morbidity associated with unnecessary surgery resulting from false positive screening results. Acceptability and compliance are crucial issues if ovarian cancer

screening were to become a national programme. While the levels of compliance reported in the literature are encouraging, one must be cautious about extending it to the wider population as recruitment into most trials are by self-referral^{5 22 23} Large randomised trials are now underway in the general population to provide definitive data on impact of screening on mortality and address morbidity, health economics and psychosocial issues. High-risk women who request screening should be counselled about the current lack of evidence of its efficacy and encouraged to participate in research trials.

9 OVARIAN CANCER RISK IN POSTMENOPAUSAL WOMEN WITH CA125 ELEVATION

9.1 Introduction

Although the definitive role of serum CA125 in screening remains to be ascertained, there is evidence that elevation is associated with an increased risk of ovarian cancer. Based on data collected in the course of the initial Bart OCS trial of 22,000 women, it was previously reported that asymptomatic postmenopausal women with a CA125 ≥ 30 U/ml have a 36 fold increased risk for diagnosis of ovarian cancer in the subsequent year.⁵¹ A further analysis was carried out to quantify the value of pelvic ultrasound in refining the risk of cancer amongst asymptomatic women with CA125 elevation.

9.2 Methods

9.2.1 Subjects

Women, aged ≥ 45 years and with 12 months of amenorrhoea were invited in 1986 to participate in a multimodal ovarian cancer screening programme.^{8 51 52 148} Exclusion criteria included previous history of ovarian cancer, bilateral oophorectomy, active malignancy or a family history of ovarian cancer involving two or more first degree relatives.

Approval was obtained from the local ethics committee and all volunteers gave written consent.

9.2.2 Trial design

22,000 postmenopausal women, aged ≥ 45 years underwent prevalence screening using CA125 between 1986 and 1989. Volunteers with a CA125 level ≥ 30 U/ml were referred for an ultrasound scan and a gynaecological evaluation if an abnormality was detected. Subsequent to the prevalence screen, the women were randomised to control and study arm. The 10,958 randomised to study arm underwent 3 annual incidence screens

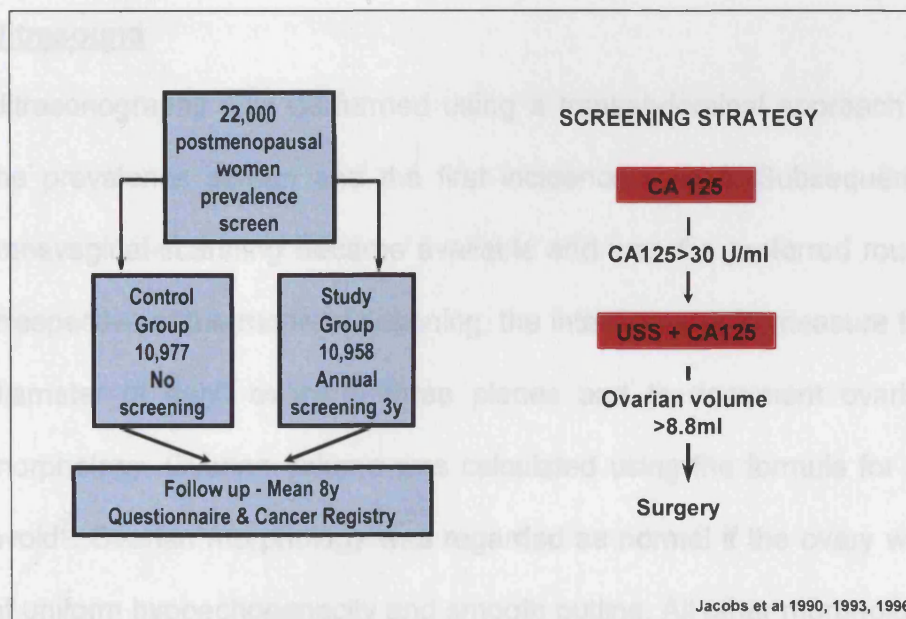


Figure 9-1: Trial design of the Bart's initial OCS trial (A)

9.2.3 Screening tests

CA125

The women were posted venepuncture equipment and asked to visit their general practitioners for venepuncture. Blood samples were sent by first class mail to the Ovarian Cancer Screening Unit. On receipt at the laboratory, the samples were centrifuged at 4,000 rpm for 10 minutes and the serum separated, aliquot prepared and stored at -20°C. All blood samples over 56 hours since venepuncture were discarded. Serum CA125 levels were determined by commercial radioimmunoassay within two weeks of receipt of the blood sample.

Ultrasound

Ultrasonography was performed using a transabdominal approach in the prevalence screen and the first incidence screen. Subsequently transvaginal scanning became available and was the preferred route. Irrespective of the mode of scanning, the intention was to measure the diameter of each ovary in three planes and to document ovarian morphology. Ovarian volume was calculated using the formula for an ovoid⁷. Ovarian morphology was regarded as normal if the ovary was of uniform hypoechogenicity and smooth outline. All other morphology was regarded as abnormal.

9.2.4 Screening strategy

All women in the prevalence screen and those in the screen arm following randomisation underwent an annual serum CA125 measurement. If the serum CA125 was $<30\text{U/ml}$, it was regarded as normal. If the serum CA125 was $\geq 30\text{ U/ml}$, it was regarded as abnormal and the women were asked to attend for an ultrasound scan. The interpretation and management protocol following ultrasound assessment was as follows:

- (1) Normal scan - (a) Ovarian volume $<8.8\text{ml}$ with normal morphology (uniform hypoechogenicity and smooth outlines) or (b) Ovaries not visualised but no pelvic abnormality apparent: repeat CA125 estimation every three months for a year and then return to annual screening.
- (2) Equivocal scan - Ovarian volume $<8.8\text{ml}$ and abnormal morphology: repeat scans at intervals of 6 weeks until a scan could be classified as normal or abnormal.
- (3) Abnormal scan - Ovarian volume $\geq 8.8\text{ml}$, irrespective of ovarian morphology: referral to a gynaecologist for assessment and advice. Management including surgical intervention, was at the discretion of the specialist receiving the referral.

9.2.5 Follow Up

In December 1997, all volunteers were traced via the National Health Service Central Register to document cases of cancer which had occurred in this population¹². In addition, all volunteers were followed up annually during the study by a questionnaire which specifically enquired about any hospital visits in the previous year. When a reply suggested a possible gynaecological malignancy, histopathological and clinical information was obtained from the general practitioner and/or hospital.

9.2.6 Case Ascertainment

An independent pathologist who had no knowledge of the randomisation status reviewed all reports and histological slides. Only women confirmed to have primary, invasive epithelial ovarian or fallopian tube cancer (index cancers) were included as cases.

9.2.7 Analysis

As part of the work undertaken in the course of this thesis, a database was built and all the details documented on the ultrasound scans performed in women with elevated serum CA125 in the course of Bart's trial A were entered. The scans were classified as per trial protocol. In addition, ovarian morphology was reclassified into normal if

the ovary was of uniform hypoechogenicity and smooth outline, simple cyst if a single, thin walled, anechoic cyst with no septa or papillary projections was detected or complex which included all abnormal ovarian morphology other than simple cysts.

Index cancers were defined as primary invasive epithelial carcinomas of the ovary and fallopian tube.⁵¹ The risk of index cancer at time interval t from the date of ultrasound in volunteers with scans satisfying a particular ultrasound criterion (abnormal ovarian morphology and volume over a specified cut-off) was calculated by dividing the number of volunteers with scans satisfying that criterion who developed index cancers within time t by the total number of volunteers with scans satisfying the criterion. Cumulative risk curves were constructed by plotting the calculated risk values against time. The observed risk of index cancer for all 22,000 study volunteers as well as for all volunteers with CA125 > 30U/ml at a given time interval t had been previously calculated.⁵¹ The relative risks of cancer at 1 and 5 years were computed by dividing the calculated risk for women satisfying a specified ultrasound criterion at 1 and 5 years by the observed risk for the entire study population at 1 and 5 years respectively. Confidence intervals for the risk estimates and the relative risk estimates were calculated using the Taylor series method.

9.3 Results

Of the 22,000 study participants, 741 had a CA125 >30 U/ml and underwent a scan. A further 26 volunteers with a CA125 >30 U/ml declined an ultrasound (n=15) or were found to be premenopausal (n=11) and were therefore not included in the analysis. Twenty index cancers were diagnosed amongst the 741 women with a CA125 >30 U/ml during a median follow up of 6.8 years. The index cancers were invasive epithelial cancers of the following histological types; serous (7), endometrioid (6), clear cell (2), undifferentiated (1), fallopian tube (3). The number of index cancers at FIGO (International Federation of Gynaecology and Obstetrics) stages I, II, III and IV were 7, 1, 9 and 2 respectively. The histological type and precise stage were not known for one patient whose diagnosis was on the basis of imaging findings, clinical assessment, and an ascitic tap which revealed adenocarcinoma cells.

Of the 741 women, 662 women had normal ovarian morphology on scan and only one had a subsequent diagnosis of an index cancer (at 2.3 years of follow up). Of the 79 women with abnormal ovarian morphology, 19 had a subsequent diagnosis of an index cancer. Of the women with abnormal morphology and an ovarian volume >20ml and >100ml, 15/41 and 10/17 respectively had a subsequent diagnosis of an index cancer. Figure 9-2 shows the relation between cumulative risk of developing an index cancer according to CA125 and ultrasound

findings. Compared to the entire study population (curve A), women with a CA125 ≥ 30 U/ml (curve B) had an increased risk of developing an index cancer. However, the subgroup of women with an elevated CA125 but normal ovarian morphology (curve C) had a similar cumulative risk to the entire study population (Jacobs et al, 1996) (0.15% vs. 0.22%, 95% confidence intervals [CI] 0.02-1.12 vs. 0.18-0.30). In contrast the cumulative risk of developing index cancer in women with a CA125 >30 U/ml and abnormal morphology (curve D) was 24% (CI: 15-38). Further stratification of risk assessment was achieved by incorporating volume measurements in addition to morphology. The cumulative risk for index cancer in women with CA125 ≥ 30 U/ml associated with abnormal morphology and ovarian volume of >20 mls (curve E) and >100 mls (curve F) was 37% (CI 22-61) and 59% (CI 32-111) respectively.

The relative risk (RR) of an index cancer at 1 and 5 years follow up for various criteria are shown in Figure 9-2. Among volunteers with a raised CA125 and abnormal ovarian morphology, the relative risk of index cancer at one year was 327 compared to the entire study population (RR 1.0). The highest relative risk at one year follow up was for women with a CA125 >30 U/ml whose ultrasound revealed abnormal morphology and ovarian volume >100 ml (RR 809, CI 302-2165). Further stratification of women with abnormal ovarian morphology on the basis of CA125 level revealed that the 29 with

OVARIAN CANCER RISK

CA125 ≥ 50 U/ml had a RR of 664 (CI 277-1590) and the 10 with a CA125 ≥ 100 U/ml had a RR of 1682 (CI 486.5-5816).

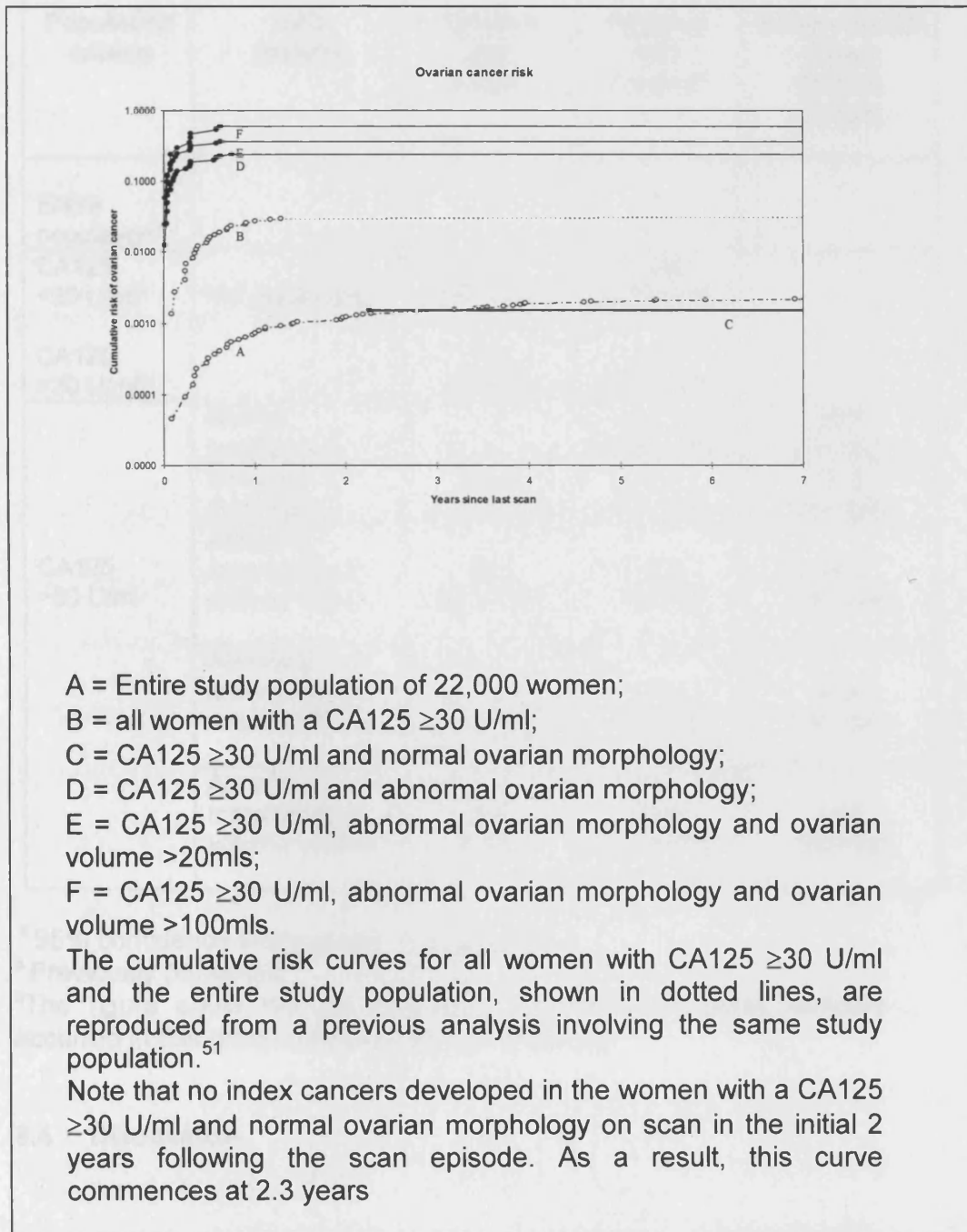


Figure 9-2: Cumulative risk of developing an index cancer according to CA125 and ultrasound in asymptomatic postmenopausal women

Table 9-1: Relative risk of index cancer at 1 and 5 years follow up for various ovarian ultrasound criteria

Population criteria	USS criteria	Relative risk 1 year ^a	Relative risk 5 years ^a	Serum CA125 (U/ml) Median (range)
Entire population ^b		1	1	
CA125 <30 U/ml ^b	Not applicable	0.13 (0.03-0.58)	0.54 (0.32-0.91)	
CA125 >30 U/ml ^b		36 (18-70)	14.3 (8.5-24)	
CA125 >30 U/ml	Normal morphology	^c	0.76 (0.09-5.96)	35.6 (30-318)
	Abnormal morphology	327 (150-708)	119 (56-244)	39.2 (30->500)
	Abnormal morphology & volume >20 ml	503 (218-1164)	183 (83-402)	39.9 (30->500)
	Abnormal morphology & volume >50 ml	617 (254-1495)	224 (97-518)	40.6 (30-134)
	Abnormal morphology & volume >100 ml	809 (302-2171)	294 (114-756)	40.6 (30-108)

^a 95% confidence limits shown in parenthesis.

^b Previously published.⁵¹

^c The figure could not be calculated because no index cancers occurred in this group until 2.3 years of follow up.

9.4 Discussion

We have previously reported that asymptomatic postmenopausal women with a CA125 level ≥ 30 U/ml have a 36 fold increased risk of ovarian cancer compared to the general population.⁵¹ This finding

justified close surveillance of all postmenopausal women undergoing ovarian cancer screening who were found to have an elevated serum CA125. In the Bart's A trial this surveillance was undertaken using pelvic ultrasonography. The incidence of ovarian cancer on long term follow up and the details of ultrasound findings in the study made it possible to assess the impact of ultrasound on ovarian cancer risk stratification. The findings indicate that women at increased risk on the basis of an elevated CA125 can be further stratified for ovarian cancer risk according to ultrasound findings.

The majority (89%) of women with an elevated CA125 had normal scan findings. None of these women developed an index cancer within one year and only 1/662 during the full duration of the study follow up. This group of women were not at increased risk of an index cancer compared to the general population despite their CA125 elevation. In contrast, women with a raised CA125 and abnormal ultrasound findings are at a markedly increased risk of an index cancer. The risk of index cancer during the subsequent year for women with a CA125 ≥ 30 U/ml and abnormal ovarian morphology on scan was 300-fold that of the entire population. This risk is significantly higher than the risk associated with an elevated CA125 alone⁶. In view of the documentation of this high risk, the combination of CA125 elevation and abnormal ovarian scan findings justifies prompt investigation even when found in asymptomatic women.

Further risk stratification was possible on the basis of ovarian volume measurements at ultrasound. Asymptomatic postmenopausal women with a CA125 ≥ 30 U/ml, abnormal ovarian morphology and an ovarian volume > 100 ml were at 800 fold increased risk of developing an index cancer during the subsequent year. Risk stratification, according to the details of morphological findings may be valuable but was not feasible within the size of our dataset. Further analysis suggested that within the small group of women with abnormal ovarian morphology, the risk of ovarian cancer could be further categorised according to CA 125 level.

The impact of screening for ovarian cancer on mortality is still uncertain. Furthermore, screening has a well documented false positive rate which can result in anxiety and morbidity associated with surgical investigation. For these reasons, ovarian cancer screening should be limited to women at high risk because of a strong family history and women participating in research trials. Nevertheless, inappropriate screening is performed and clinicians are increasingly faced with the problem of CA 125 elevation in asymptomatic women. The results of this analysis provide some guidance for management of postmenopausal women in this situation. It is clear that ultrasound can separate asymptomatic postmenopausal women with raised CA125 levels into those who have normal scans and are not at increased risk of ovarian cancer and those with abnormal scans who are at substantially increased risk of ovarian cancer.

10 REFINING THE ULTRASOUND ALGORITHM

10.1 Introduction

The group had previously demonstrated that the poor performance characteristics of serum CA125 and pelvic ultrasound as individual tests in ovarian cancer screening can be overcome by a sequential screening strategy (multimodal strategy) using serum CA125 as the primary screen and ultrasound as the secondary test in the Bart's A trial. Using this multimodal strategy to screen postmenopausal women from the general population, positive predictive values of 26% and 21% were achieved at initial prevalence screening and on annual incidence screening respectively.^{8 52} When these trials were initiated, no data was available regarding ultrasound findings in postmenopausal women with elevated serum CA125. The definition of a normal scan was therefore based on ovarian volume criteria reported by Campbell et al in a study which used ultrasound to measure ovarian volume in normal postmenopausal women.¹⁵⁹ The current project was undertaken in order to assess the performance characteristics of pelvic ultrasound and to refine the crude criteria used for interpretation of ultrasound findings in this multimodal screening strategy.

10.2 Method

The data from the Bart's A trial was collated and databased as described in the preceding chapter (Chapter 9)

Analysis

Scans were grouped into episodes for the purpose of analysis. An episode was defined as a single or series of scans initiated by a raised CA125 and ending in referral for a gynaecological opinion or return to annual CA125 screening. Study participants underwent a maximum of four CA125 screens (1 prevalence and 3 incidence) and hence a maximum of 4 episodes were possible per volunteer. For analysis, each scan episode was classified on the basis of last scan result into normal, equivocal or abnormal. Index cancers were defined as primary invasive epithelial carcinomas of the ovary and fallopian tube.⁵² Sensitivity, specificity, and positive predictive value for detection of index cancer were calculated as shown in Table 10-3.

10.3 Results

Of the 22,000 study subjects who participated in the trial, a total of 741 subjects with an elevated CA125 underwent a total of 1219 scans. A further 26 subjects with a CA125 ≥ 30 U/ml are not included as they declined a scan (n=15) or were found to be pre-menopausal (n=11). Of the 741 subjects, 475, 128, 87 and 51 had 1, 2, 3 or > 3 scans respectively. 918 of the 1219 scans (75.3%) were performed transabdominally, 103 (8.4%) transvaginally and 198 (16.2%) both transabdominally and transvaginally.

25 of the 741 women had previously undergone unilateral oophorectomy. 44 of the 1219 scans were performed on these 25 women. As a result, the overall number of ovarian scans attempted was 2394. The ovary was visualised in 2129 (89%) of the 2394 scans. Ovarian dimensions were documented in 1839 (86%) of the scans where visualisation was possible. The mean ovarian volume calculated from the 1663 scans of ovaries that were normal on follow up was 2.57cm³ (standard deviation 3.1cm³). A total of 1027 scan episodes resulted of which 97 (9.4%) were abnormal or equivocal Table 10-1.

Table 10-1: Number of scans and classification of scan episodes in women with elevated CA125 levels

Classification of scan episodes	No. of women	No. of scan episodes	No. of scans
Normal	645	930	1072
Equivocal	16	17	27
Abnormal	80	80	120
Total	741	1027	1219

Ultrasound findings and outcome on follow up are summarised below (Table 10-2).

Normal scan episodes: There were a total of 930 normal episodes. Thirteen subjects underwent surgical investigation despite normal ovarian findings. In nine cases, this was for incidental findings of a thickened endometrium (n=4), uterine fibroids (n=4) and a bladder abnormality (n=1) which resulted in the detection of one endometrial

and one bladder carcinoma. A further four subjects were referred for a specialist opinion and eventually underwent surgery as they were anxious following CA125 elevation. Surgery revealed no abnormality (3) and pelvic adhesions (1). Only one woman with a normal scan episode developed ovarian cancer which was diagnosed 2.25 years after her last scan.

Equivocal scan episodes: There were 17 equivocal scan episodes. All the women were referred for a gynaecological assessment. In 9/17 episodes, volunteers with persistent simple cysts, elected not to have surgery. They continued to undergo annual CA125 screening and did not develop index cancers on follow up. Two women with equivocal results died before a repeat scan, one from pneumonia and the other from ovarian cancer (diagnosed on the basis of clinical findings and an ascitic tap). The remaining six volunteers with equivocal episodes underwent surgical investigation which revealed ovarian cancer in one case and benign pelvic pathology in the five other cases.

Abnormal episodes: There were 80 abnormal episodes. In 17/80 episodes, abnormal ovarian volume was associated with normal morphology (22 scans, 17 volunteers). Only one of these 17 volunteers underwent surgery and she had a benign ovarian thecoma. The other 16 subjects did not undergo surgical investigation following clinical decisions based on borderline increases in ovarian volume (n=10), falling CA125 levels (n=3), diminishing ovarian volume on serial

scanning (n=2) and anaesthetic risk (n=1). None of these subjects developed ovarian carcinoma. In 63/80 episodes, both ovarian volume and morphology were abnormal (98 scans, 63 volunteers). Five of these 63 episodes involved volunteers with stable CA125 levels on serial measurements and simple cysts (ovarian volume 10.24-29.7cm³). In these cases, a clinical decision was made not to proceed to surgery and all these volunteers have remained well. The remaining 58/63 episodes resulted in surgical referral which revealed index cancer in 17 cases. The remaining 41 subjects had adenocarcinoma of unknown primary (2), benign pelvic pathology (31) and no abnormality (8)

Table 10-2: Ultrasound episodes and outcome on follow up.

Episodes (morphology)	Outcome					
	Index cancer	Other cancers	Benign ovarian lesions	Other benign pelvic lesions	Normal	Total
Normal	1*	2	0	8	920	930
Equivocal						
(Simple cyst)	1	0	3	0	10	14
(Complex mass)	1**	0	0	2	0	3
Abnormal						
(Normal morphology)	0	0	1	0	16	17
(Simple cyst)	2	0	10	1	10	23
(Complex mass)	15	2***	15	5	3	40
Total	20	4	29	16	959	1027

*Developed ovarian cancer 2.25 years after normal scan

**Died before surgery was undertaken;

***Both were adenocarcinomas of unknown primary.

The performance of different ultrasound criteria for detecting the 19 index cancers diagnosed within 1 year of an ultrasound is shown in Table 10-3. Abnormal morphology achieved higher sensitivity (100%) than abnormal volume (89.5%) or complex morphology (84%). However, the differences were not statistically significant. Similarly, the positive predictive value of 37.2% achieved by using complex morphology was not significantly higher than that achieved by abnormal morphology (23.8%) or abnormal volume (21.3%).

Table 10-3: Performance characteristics of ultrasound for detection of index cancers diagnosed within one year of screening in women with elevated serum CA125.

	Index cancer	No index cancer	Sensitivity, specificity, positive predictive value (PPV)
Criteria abnormal	a	c	Sensitivity = $a / a+b$
Criteria normal	b	d	Specificity = $d / c+d$
Abnormal volume	17	63	PPV = $a / a+c$
Normal volume	2	945	Sensitivity = 89.5%
			Specificity = 93.75%
			PPV = 21.3%
Abnormal morphology	19	61	Sensitivity = 100%
Normal morphology	0	947	Specificity = 93.95%
			PPV = 23.75%
Complex morphology	16	27	Sensitivity = 84.2%
Normal morphology	3	981	Specificity = 97.32%
OR simple cyst			PPV = 37.21%

10.4 Discussion

This is the first detailed report of ultrasound findings in asymptomatic postmenopausal women with an elevated serum CA125. A limitation of the current study was the use of transabdominal scanning in the initial phase. It is possible that the sensitivity for detection of morphological abnormalities was underestimated as a result. Nevertheless, the findings have important clinical implications and are valuable for the design of future ovarian cancer screening trials.

The performance of ultrasound in the prospective study was encouraging and a variety of ultrasound criteria achieved an acceptable positive predictive value. Strict application of the study criteria (ovarian volume ≥ 8.8 ml) without clinical input would have resulted in surgical referral following 80 scan episodes, with a sensitivity of 89.5% and a positive predictive value of 21%. Using abnormal morphology as the discriminating criterion increased sensitivity to 100% with minimal change in specificity and positive predictive value but this improvement did not reach statistical significance. It is, however, worth noting that both the 2 index cancers that had normal ovarian volume had abnormal morphology.

The use of complex morphology further increased specificity and positive predictive value but again statistical significance was not achieved. Using complex morphology, sensitivity fell to 84% as three

index cancers appeared to be simple cysts on transabdominal scanning. This may be attributable to the lower resolution of the older generation transabdominal scanning techniques used in the early part of the study compared to the transvaginal approach now in use. This is consistent with the observation that 5 of the 12 ovarian cancers detected on primary transabdominal ultrasound screening in the study by Campbell et al¹⁶⁰ were found to have simple morphology on scan while none of the ovarian cancers detected by transvaginal scanning in the more recent ultrasound screening trials^{114 121} had simple morphology. In the Kentucky study, 256 postmenopausal women were detected to have simple ovarian cysts <10cms in diameter and none developed an ovarian malignancy.¹⁰⁸

The use of ultrasound assessment as a secondary test maintains the sensitivity of the CA125 algorithm and enables the overall screening programme to achieve a high positive predictive value. Clearly, a variety of ultrasound criteria can achieve high sensitivity and positive predictive value for index cancers in women with an elevated CA125. The balance of evidence suggests that ovarian morphology is the most sensitive criteria. Larger studies are needed to definitively establish the criterion with the best performance characteristics. As a result of this analysis, the ultrasound algorithm in the Bart's B trial (detailed in chapter 11) was refined to incorporate both ovarian morphology and volume, with the major emphasis on morphology. In the current definitive trial, United Kingdom Collaborative Trial of Ovarian Cancer

Screening (UKCTOCS), the ultrasound algorithm is solely based on morphology, although volume is recorded.

11 A PILOT TRIAL USING THE 'ROC' ALGORITHM

11.1 Introduction

In 1993, the group demonstrated in the prospective trial of 22,000 postmenopausal women (Bart's A) from the general population that a multimodal OCS strategy can achieve a sensitivity of 78.6%, specificity of 99.9% and positive predictive value of 26.8% for detection of OC¹. In this trial, the serum CA125 was interpreted using a fixed cut-off of 30 U/l. Analysis of the data revealed that serial CA125 values prior to detection of ovarian cancer exhibited increasing levels following a change-point while for almost all other subjects CA125 values had a flat profile which fluctuated around an individual's own baseline level. Interpreting this additional information in serial CA125 values using longitudinal statistical models retrospectively increased the sensitivity for detection of ovarian cancer from 70% to 86%⁵⁵, while maintaining a high level of first line specificity (98%) for referral to ultrasound exceeding that of the fixed CA125 cut-off. The model estimates an individual's 'Risk Of Ovarian Cancer' (ROC) starting with an estimate based on age and modified by the relative fit of the serial CA125 profile to the change-point model estimated from known cases compared to the flat profile model estimated from known controls¹⁶¹. The screening algorithm interprets an individual's CA125 values by calculating the ROC and making screening decisions, such as returning to annual screening, repeating the CA125 test within a shorter period of time, or referral to ultrasound, on the basis of the ROC value.

Parallel to this effort, analysis of the ultrasound data from the trials established that refining the ultrasound criteria could increase specificity (chapters 10)^{53 54}. Complex ovarian morphology was the best predictor of ovarian cancer in asymptomatic postmenopausal women found to have an elevated serum CA125 level. This was incorporated into the new strategy.

A prospective pilot screening trial using the new Risk of Ovarian Cancer Algorithm (ROCA) incorporating the ROC calculation for CA125 interpretation and refined ultrasound criteria was set up to inform the design of a definitive RCT. The chapter describes the outcome of the prevalence screen in this trial and provides the first data on prospective use of the ROC algorithm in ovarian cancer screening.

11.2 Methods

11.2.1 Subjects

Approval was obtained from the local ethics committee. Women from England, Scotland, and Wales were invited to volunteer via articles in the press and leaflets distributed through collaborating general practices and occupational health departments of major companies. In addition, invitations were sent to those who had participated in our previous screening studies.⁸

⁵² Women who expressed interest were sent a detailed fact sheet describing the study and a recruitment appointment at the Ovarian Cancer Screening Unit at Bart's Hospital or at their general practice. At these

appointments, the study design was explained and volunteers completed a questionnaire and gave written consent. Volunteers were eligible if they fulfilled the following criteria: (a) Age ≥ 50 years, and (b) >12 months amenorrhoea following a natural or surgical menopause or >12 months of hormone replacement therapy commenced for menopausal symptoms. The exclusion criteria were: (a) History of bilateral oophorectomy. (b) Active malignancy (women with a past history of malignancy were eligible if they had no documented persistent or recurrent disease). (c) Increased risk of ovarian cancer due to familial predisposition – exclusion criteria were entry criteria for the UK Familial Ovarian Cancer Screening Study (d) Previous history of ovarian cancer.

11.2.2 Trial design

Eligible volunteers were randomised with equal chance to either the control or screening group using a computerised random number generator. All volunteers randomised to the screening group underwent primary screening (Level I) with CA125. If an abnormality was detected the women had secondary screening (Level II) using CA125 and transvaginal ultrasound (TVS) of the ovaries (Figure 11-1). A customised database was built for the trial that assessed eligibility and undertook randomisation, 'Risk of Ovarian Cancer' calculation, classification of results and letter printing.

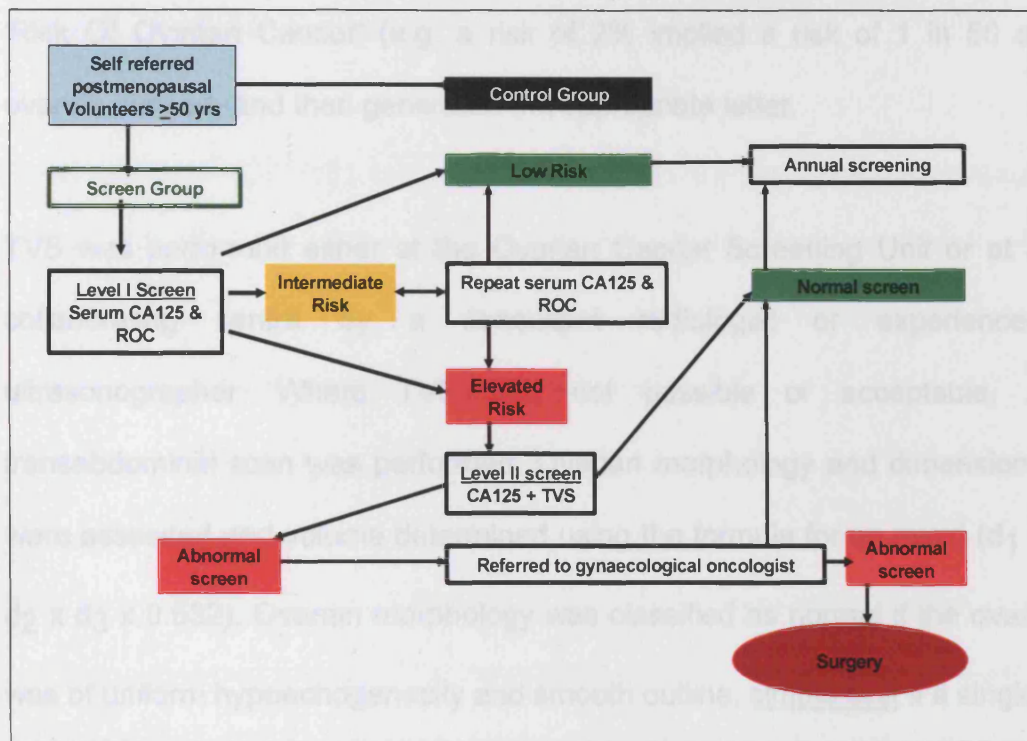


Figure 11-1: Design of Bart's B pilot RCT

11.2.3 Screening tests

The women in the screening group were posted venepuncture equipment and asked to visit their general practitioners for venepuncture. Blood samples were sent to the Ovarian Cancer Screening Unit by first class mail, centrifuged at 4,000 rpm for 10 minutes and the serum separated, aliquots prepared and stored at -20°C. All blood samples received >56 hours after venepuncture were discarded and repeat samples requested. Serum CA125 levels were determined by commercial radioimmunoassay (CA 125II kit, Centocor, Malvern PA) within two weeks of receipt of the blood sample. The CA125 values were entered into the trial database, which calculated the

'Risk Of Ovarian Cancer' (e.g. a risk of 2% implied a risk of 1 in 50 of ovarian cancer), and then generated the appropriate letter.

TVS was performed either at the Ovarian Cancer Screening Unit or at a collaborating centre by a consultant radiologist or experienced ultrasonographer. Where TVS was not possible or acceptable, a transabdominal scan was performed. Ovarian morphology and dimensions were assessed and volume determined using the formula for an ovoid ($d_1 \times d_2 \times d_3 \times 0.532$). Ovarian morphology was classified as normal if the ovary was of uniform hypoechogenicity and smooth outline, simple cyst if a single, thin walled, anechoic cyst with no septa or papillary projections was detected and complex if there was non-uniform echogenicity due to cystic and solid areas in the ovary, multiple cysts or ascites. The larger of the two ovaries with the most abnormal morphology was used to classify scans as shown in Table 11-1.

Table 11-1: Classification of scans

Volume	SCAN CLASSIFICATION		
	Morphology		
	Normal*	Simple cyst	Complex
≤10ml	Normal	Equivocal	Equivocal
10 to 60mls	Equivocal	Equivocal	Abnormal
≥ 60 mls	Abnormal	Abnormal	Abnormal
Not visualised due to poor view of pelvis	Unsatisfactory		

* Scans where the ovaries were not visualised but a good view of the pelvis and iliac vessels was obtained and no abnormality was seen were included under normal.

11.2.4 Screening strategy

Level I screen (CA125): Women in the screen arm underwent an annual serum CA125 assay interpreted using the 'Risk Of Ovarian Cancer' calculation. On the basis of the risk value, volunteers were allocated to one of three groups and managed as detailed below:

- (1) Normal Risk (<1 in 2000): Volunteers were informed that their results were normal.
- (2) Intermediate Risk (1 in 2000 – 1 in 500): Volunteers were recalled for a repeat venepuncture. The interval of recall varied between 6 weeks and 6 months and was inversely related to the risk estimate. Management following repeat testing depended on the recalculated risk value which incorporated the latest CA125 result.
- (3) Elevated Risk (>1 in 500): Volunteers were recalled for a Level II screen.

Level II screen (TVS and CA125): Women underwent a scan of their ovaries and serum CA125 assay. Based on the results of these tests, they were managed as shown in Table 11-2:

- (1) **Normal scan and risk <1 in 25 (Green)** - Volunteers were informed that their results were normal.
- (2) **Normal scan and risk 1 in 25 - 1 in 5 (Yellow)** - Serum CA125 was repeated and the risk reassessed. Subsequent management was determined by the same risk criteria as described above for Level 1 screens.

- (3) **Equivocal or Unsatisfactory scans irrespective of the risk value or Normal scan with risk >1 in 5** (Orange) – TVS and CA125 were repeated after ruling out other conditions associated with a CA125 elevation. The volunteer was referred for surgery if the scan findings were persistently equivocal or became abnormal.
- (4) **Abnormal scans irrespective of the risk value** (Red) - The volunteer was referred to a gynaecological oncologist for assessment and possible surgical investigation.

Table 11-2: Management of women following Level 2 screen

ROC value	Classification of scans			
	Abnormal	Equivocal	Unsatisfactory	Normal
<1 in 25	Referral	Repeat CA125 and TVS		Annual screening
1 in 25 - 1 in 5				Repeat CA125
>1 in 5				

11.2.5 Confirmation of diagnosis

Operative notes and histology reports of those who underwent surgery were reviewed to confirm diagnosis and the stage, grade and histology of any cancer diagnosed. Further information regarding the women diagnosed with ovarian cancers was obtained from the surgeon, medical oncologist, and general practitioner.

11.2.6 Follow up

All volunteers who did not undergo surgery or had not withdrawn from the study were contacted a year later for further screening and were sent a postal follow up questionnaire 3 years after recruitment.

11.2.7 Analysis

The end point of the prevalence screen was defined as surgery following referral to a specialist or return to annual screening. The prevalence screen therefore consisted of a single or series of serum CA125 / scans culminating in surgery or return to annual screening. Index cancers were defined as primary invasive epithelial carcinomas of the ovary and fallopian tube. For the purpose of this analysis, all volunteers have been censored one year after the date of the final blood or scan test related to their prevalence screen. Their status with regard to a diagnosis of an index cancer was determined on the date of censorship. Specificity and positive predictive value for detection of index cancer has been calculated as shown in Table 11-7.

11.3 Results

A total of 13,582 women were recruited in the UK between 1995 and 2000 (Figure 11-2). 50 women provided incomplete data. 66 women were ineligible, the majority (51) because they were pre-menopausal. Of the

remaining, 6682 were randomised to the screen arm. Table 11-3 summarises their baseline characteristics.

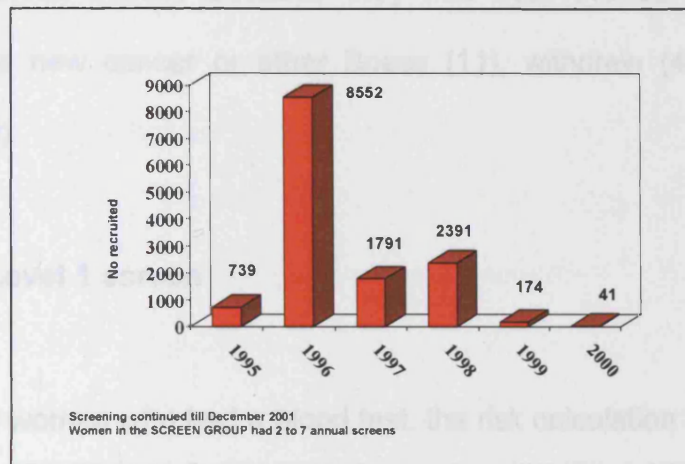


Figure 11-2: Recruitment in the Bart's B trial

Table 11-3: Baseline characteristics of study population

	Median (25 th -75 th centiles)
Age	59.65 (55.57 - 64.17)
Years since last period	10.1 (5.5 - 16.08)
Duration of HRT use in those who were currently on HRT (yrs)	5.02 (2.58 - 7.52)
Duration of OCP use (yrs) in those who had used it	4 (1 - 10)
Miscarriages	1 (1-2)
No. of children	2 (2-3)
Height (cms)	162.56 (157.48 - 167.64)
Weight (kg)	64.86 (59.42 - 73.03)
	Number (%)
Ever use of OCP	4746 (35.3%)
Current use of HRT	4671 (34.7%)
Personal history of cancer	689 (5.1%)*
Personal history of breast cancer	315 (2.3%)
Maternal history of ovarian cancer	283 (2.1%)
Maternal history of breast cancer	483 (3.6%)
Hysterectomy	2580 (19.2%)
Ethnicity	
White	12232 (90.9%)
Black	33 (0.3%)
Asian	24 (0.2%)
Other**	1171 (8.7%)

* includes those with personal history of breast cancer

** includes women who did not fill in ethnicity

Of the women in the intermediate group, 1131 were returned to annual screening, 44 withdrew, and 53 were found to have elevated risk. All 144 women (91 + 53) with an elevated risk (i.e. risk >1 in 500) were offered a Level II screen. If a fixed cut-off of CA125 >30U/ml had been used, 413 women would have required a Level II screen.

11.4.2 Level II screen and further management

Six of the 144 women in the elevated risk group were found to have non-ovarian malignancies - myeloma, hepatocellular carcinoma, colon, breast, endometrial cancer, and adenocarcinoma of unknown primary. In the latter case the woman had a risk estimate of >1 in 5 with normal ovaries on scan. On CT, she had ascites with a large splenic mass, extensive upper abdominal lymphadenopathy, a 2cm right external iliac mass and masses in the upper body of stomach and lower lobe of right lung but no pelvic abnormality. Biopsy of a lymph node confirmed metastatic adenocarcinoma and the diagnosis on multidisciplinary review was of abdominal carcinomatosis of unknown primary origin.

The results of the Level II screen in the remaining 138 women were classified as shown in Table 11-4 with the overall outcome summarised in Figure 11-4.

- (1) **Normal scan and risk <1 in 25** (Green): All 39 participants in this group returned to annual screening.

- (2) **Normal scan and risk 1 in 25 - 1 in 5 (Yellow)** : All 28 women had a further CA125 and were then returned to annual screening.

- (3) **Equivocal or Unsatisfactory scans irrespective of the risk value or Normal scan with risk >1 in 5**

(Orange): All 58 had a repeat CA125 and TVS. Six underwent surgery as the repeat TVS was abnormal (2) or persistently equivocal (4). 52 returned to annual screening

- (4) **Abnormal scans irrespective of the risk value (Red)**: 13 women were assessed clinically and 10 underwent surgery. Three women (RISK values <1%) were managed conservatively; one had a diagnosis of uterine fibroids, a second had a biloculated small ovarian cyst with no sinister features and the third had multicystic ovaries with the diameter of the largest cyst <2cms. The latter was followed up with repeat scans and bloods for 6 months during which time the ovarian size decreased.

Table 11-4: Results of Level II screen

ROC value	Classification of scans				Total
	Abnormal	Equivocal	Unsatisfactory	Normal	
<1 in 25	4	2	21	39	66
1 in 25 – 1 in 5	1	2	1	28	32
>1 in 5	7	2	4	26	39
No blood test	1				1
Total	13	6	26	93	138

11.5 Surgery in screen positives

Overall, 16 women underwent surgery as a result of prevalence screening. 11 had surgery at Bart's Hospital, London and 5 had surgery in other hospitals following referral by their general practitioner. Seven had a laparotomy, 4 a diagnostic laparoscopy and 5 a laparoscopic salpingo-oophorectomy. Two of the latter had completion laparotomy as they were found to have ovarian cancer. Postoperatively one woman (without ovarian cancer) developed bowel obstruction and had to undergo a further laparotomy, with drainage of a pelvic abscess and resection of small bowel, caecum, and ascending colon.

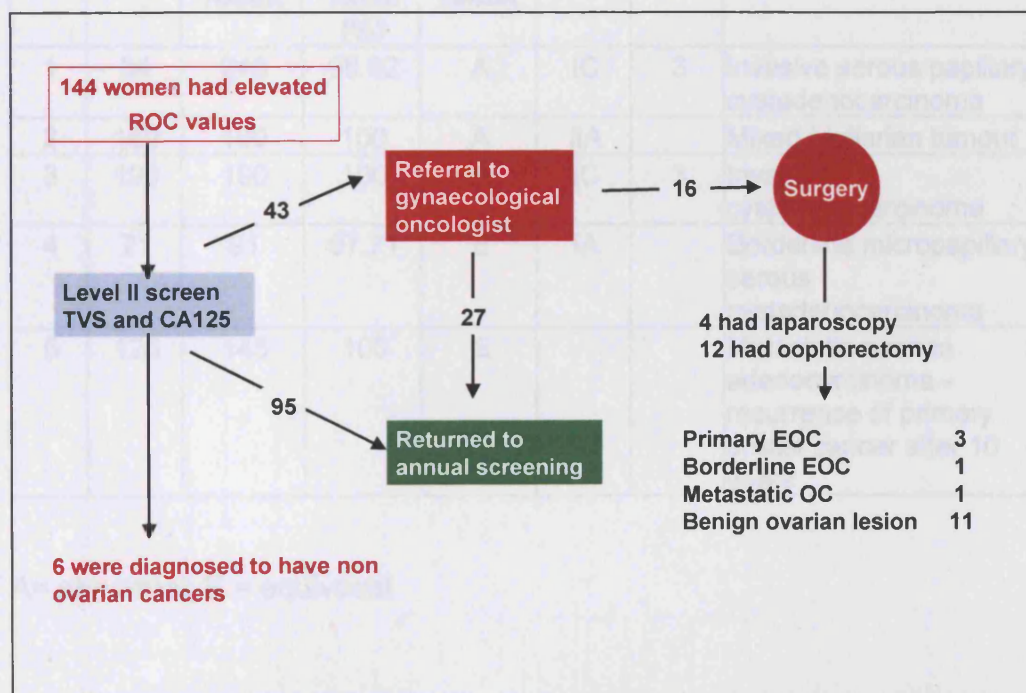


Figure 11-4: Summary of management of women with elevated ROC values on Level I screen

11.5.1 Final diagnosis in screen positives

Ovarian malignancy was detected in 5 women. One had ovarian recurrence of a breast cancer 16 years after initial diagnosis, one had a borderline papillary serous ovarian carcinoma, and 3 had primary invasive epithelial ovarian cancers (Table 11-5). The details of the benign findings in the remaining 11 women are summarised in Table 11-6.

Table 11-5: Details of women with diagnosis of ovarian cancer following surgery

No	First CA125	Final CA125 result	Final ROC value (%)	Final scan result	Stage	Grade	Histology
1	34	248	98.82	A	IC	3	Invasive serous papillary cystadenocarcinoma
2	169	160	100	A	IIA		Mixed Mullerian tumour
3	190	190	100	A	IC	3	Invasive cystadenocarcinoma
4	71	91	97.71	E	IA		Borderline micropapillary serous cystadenocarcinoma
5	125	145	100	E			Metastatic ovarian adenocarcinoma - recurrence of primary breast cancer after 10 years

A= abnormal; E = equivocal

PILOT RCT USING ROC ALGORITHM

Table 11-6: Details of women without a diagnosis of ovarian cancer following surgery

No	Final scan result	Final CA125	ROC value	Histology of removed ovaries	Other pelvic findings
1	A	54	10.24	Not removed	Pelvic adhesions
2	E	135	100	Normal ovaries	Dense adhesions -diverticulitis
3	E	53	10.89	Not removed	Pelvic adhesions
4	A	124	99.26	Bilateral serous cystadenofibroma	
5	A	25	0.47	Serous cystadenoma	
6	A	100	100	Serous cystadenoma	
7	A	62	99.98	Not removed	Fibroids, adhesions
8	A	88	93.04	Serous cystadenoma	Adhesions
9	A	117	100	Bilateral ovarian endometriosis	
10	A	65	34.67	Not removed	Pelvic adhesions - diverticulitis
11	E (4th scan)	60	0.02	Serous cystadenoma	

A = abnormal; E = equivocal

11.5.2 Follow up

Follow up data at 1 year after the final test related to the prevalence screen was available in 97.5% (6369) of the screened women. No additional cases of ovarian cancer were documented during follow up.

11.5.3 Screening Performance

The screening strategy achieved a positive predictive value of 19% (Table 11-7) for detection of primary invasive epithelial ovarian cancer. Specificity was 99.8% if all participants are included. If only those individuals who were followed for at least one year are used to calculate specificity, then it was 99.7%.

Table 11-7: Specificity and positive predictive value of the screening strategy

Result of screen and clinical assessment	Primary Invasive Epithelial OC	Not Primary Invasive Epithelial OC	Specificity (95% CI)	PPV (95% CI)
Abnormal	3	13*	99.8% (99.7- 99.9)	19% (4.1- 45.6)
Normal	0	6498		

*includes one serous papillary borderline carcinoma and one secondary ovarian carcinoma due to breast cancer recurrence.

11.6 Discussion

This chapter describes the first prospective use of the Risk of Ovarian Cancer algorithm in screening for ovarian cancer. The results demonstrate that ovarian cancer screening using the algorithm is feasible and can achieve high specificity (99.8%, 95%CI 99.7%-99.9%) and positive predictive value (19%, 95%CI 4.1%-45.6%). The initial algorithm was developed using stored serum from apparently healthy women in the Stockholm ovarian cancer screening study, six of whom were found to have ovarian cancer¹⁶². Retrospective analysis estimated it achieved a specificity of 99.7% and positive predictive value of 16% for detection of ovarian cancers diagnosed within a year of the assay¹⁶¹. The algorithm was then applied retrospectively to 33,621 CA125 results from 9,233 women from the Bart's A screening trial. When compared with a fixed cutoff for CA125, the area under the curve significantly improved from 84% to 93% ($p = 0.01$)⁵⁵. The results reported here demonstrate for the first time in a prospective study that this novel screening strategy can achieve the high specificity and PPV required for ovarian cancer screening. These are essential characteristics as positive screens result in surgical investigation, with its attendant morbidity.

The trial was undertaken to inform the design of a definitive ovarian cancer screening trial with mortality as a primary end point and to assess the feasibility and logistic implications of this approach. Based on the initial blood test, 18.8% of women had an intermediate risk value. On repeat

testing, 92% with an intermediate value were recalculated to be at normal risk and returned to annual screening. The initial protocol did not specify the number of repeat tests and 252 women were referred for 4 or more tests. Of the women recalled for 4 or more tests 6% (15/252) withdrew from the study, compared to 1.5% (18/1228) who withdrew after their first intermediate risk result (Figure 11-3). It was noted that the 15 women who withdrew after multiple tests gave the disruption and stress resulting from repeat testing as their primary reason for withdrawing. For the definitive UKCTOCS trial it was therefore decided that a maximum of three CA 125 tests would be requested and that women who remained in the intermediate group would then be offered an ultrasound scan. Assessment of anxiety and worry resulting from repeat testing is one of the core objectives of the psychosocial study that accompanies UKCTOCS.

The overall rate of referral for ultrasound assessment of the ovaries was 2.2% (144/6514), compared with a rate of 6.3% (413) had a fixed cut-off for CA125 (>30U/ml) been used. Ultrasound is an expensive and labour intensive procedure and the higher rate would have a significant impact on cost and logistics of a definitive trial and if successful, a national screening programme.

In the course of the study 6 non-ovarian cancers were diagnosed as a result of elevated CA125 levels. These included a case of adenocarcinoma of unknown primary (ACUP). The findings on imaging in this particular individual made it unlikely that the primary site was ovarian. However, the

classification of ACUP raises a difficult issue in ovarian cancer screening trials. Ovarian cancer if diagnosed at an advanced stage may wrongly be classified as ACUP resulting in a lower numbers of ovarian cancers cases (true positives). This can cause under reporting of ovarian cancer cases in the control arm of a screening trial. It is important that as much information as possible is gathered about such cases and that the number of ACUP cases in the screen and controlled arm are monitored – the numbers should not be significantly different.

Sixteen operations were undertaken following the Level II screen and clinical assessment of which 11 did not have ovarian malignancy. The major cause for false positive surgery was benign ovarian cystadenomas and the presence of pelvic adhesions. In 2 cases, this was related to diverticulitis, which is a known cause for raised CA125 levels. Initial laparoscopic assessment made it possible to avoid oophorectomy in women with normal ovaries but dense pelvic adhesions, where the risk of surgical complications may be increased.

Of the five women found to have ovarian malignancy, one had a stage IA borderline serous micropapillary ovarian cancer. There is controversy amongst trialists about inclusion of borderline tumours (tumours of low malignant potential) as 'true positives' in ovarian cancer screening trials. Recently it has been proposed that the serous borderline tumors should be classified as micropapillary serous carcinoma or atypical proliferative serous tumor. The former have a higher incidence of bilateral ovarian involvement,

recurrence with shorter progression-free interval and invasive implants. However, the overall survival of patients in both groups appear to be the same¹⁶³ and both these tumours have an overall good prognosis. We have therefore continued our practice of not including borderline ovarian carcinomas as 'true positives' irrespective of their histology as the aim is to develop a strategy that impacts on ovarian cancer mortality.

Ovarian recurrence of a primary breast cancer was detected in one patient. Women who had previously been diagnosed with a malignancy and were in remission were allowed to join the study. 5.12% (689) women in the screened arm had a personal history of cancer, mainly breast and bowel. As CA125 can occasionally be elevated in recurrences of such malignancies⁴⁸, the detection of occasional asymptomatic recurrences is inherent in the study design. The benefits of such detection are uncertain and women with a previous history of cancer should be counseled about this at recruitment.

The prevalence screen reported here involved 6532 women. Three women were diagnosed with primary invasive epithelial ovarian cancer, two Stage I and one Stage II. No other primary ovarian cancers were reported in these women during the year following their screen. The numbers are too small to comment on sensitivity or stage shift but are consistent with the data from retrospective evaluation of the Risk of Ovarian Cancer algorithm. There is preliminary evidence from our previous RCT that early detection may increase long-term survival⁸. Follow up data from prospective single arm ovarian cancer screening (OCS) trials also provide evidence of a possible

survival benefit^{9 10}. It is however important to note that the “ovarian cancers” detected by screening in the latter trials included granulosa cell and borderline ovarian carcinomas that have a good overall prognosis.

The algorithm is also being used for screening ‘high risk’ women in the US Cancer Genetics Network trial, and in the screening arm of the Gynecology Oncology Group study of women at high risk in the US. In the UK Familial Ovarian Cancer Screening Study efforts are underway to revise the current screening strategy to incorporate the ‘Risk of Ovarian Cancer’ algorithm. If screening were shown to be effective in these various trials, it is highly likely that the ‘Risk of Ovarian Cancer’ algorithm that will be part of future ovarian cancer screening programmes across the world.

12 UK COLLABORATIVE TRIAL OF OVARIAN CANCER SCREENING – TRIAL DESIGN AND ORGANISATION

12.1 Introduction

Despite advances in both surgery and chemotherapy for the treatment of ovarian cancer, there has been little mortality benefit. The relative five-year survival rate for women diagnosed in England and Wales in 1991-1993 was 29%, compared with 23% for women diagnosed 1971-1975 (www.statistics.gov.uk). In the late nineties, preliminary data from OCS trials seemed to suggest that screening and early detection may impact on OC outcome. In 1999, follow up of 22,000 women in the initial Bart's RCT of ovarian cancer screening (Bart's A) showed a significantly improved median survival (72.9 months) in women with ovarian cancer in the screened group as compared to the control group (41.8 months). The difference was not biased by lead time; ascertainment of cancers; treatment in specialist centres or follow up ⁸. Data from single arm prospective studies also suggested a possible survival benefit. The University of Kentucky Ovarian Cancer Screening Program involving nearly 15,000 women reported 92.9 +/- 6.9% survival at 2 years and 83.6 +/- 10.8% at 5 years in patients with screen detected epithelial ovarian cancer ⁹. A stage shift implying better survival was also reported from Japan where authors noted that prior to the set up of a 10 year ovarian cancer screening trial 29.7% of 35 cancers diagnosed in the department were Stage I while after the trial was initiated, 58.8% of 85 ovarian cancers treated were Stage I ¹⁰. The latter trials lack a

control group and hence are prey to a significant "healthy-volunteer effect", lead time bias, reporting bias etc. Moreover, none of the trials were designed or powered to answer definitively whether screening would have a mortality effect. With data emerging from the pilot randomised control trial (Bart's B) confirming feasibility of using the ROC algorithm in ovarian cancer screening (Chapter 7), the stage was set to conduct a large definitive screening trial with ovarian cancer mortality as the primary end point.

In 1999, a number of professional groups (the NIH Consensus Conference 1995, the Society of Gynaecologic Oncologists 1998 and the National Screening Committee in the UK 1999) were of the view that a large randomised controlled trial was required to unequivocally establish the impact of ovarian cancer screening (OCS) on disease mortality. In addition the Exceptional Cases Advisory Committee in the UK on the basis of an economic analysis and detailed systematic review¹⁶⁴ concluded that a well designed trial of OCS would be of value to the National Health Service. Lay groups like OVACOME and the National Federation of Women's Institutes urged the government to support research into OC screening. In parallel, it was clear that that there was need to perform a randomised controlled trial on the effectiveness of screening before media publicity and demand from individuals, lay groups and sectors of the medical profession led to widespread implementation of OCS.

To address these issues the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was set up and in 2001 commenced recruitment.

This chapter describes the design of the trial and its organisation.

12.2 Aims and Objectives

The overall aim of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is to provide data so that an informed decision about the introduction of population screening for ovarian cancer can be made.

Primary objective

To establish the impact of screening on ovarian cancer mortality by comparing disease mortality in the screen and control arms.

Secondary objectives

1. To assess and compare the performance characteristics of the two screening strategies (serum CA125 versus ultrasound)
2. To determine the physical morbidity resulting from surgical intervention attributable to screening
3. To assess the psychological consequences of screening
4. To determine the resource implications of screening and the resulting interventions
5. To assess feasibility of screening, as reflected by compliance rates with annual screening.
6. To establish a serum bank for future assessment of novel tumour markers.

12.3 Trial design

The design involves a randomised controlled trial of 200,000 postmenopausal women aged 50-74 years allocated in a 2:1:1 ratio to: (1) A control group (no screening) (2) A multimodal group (annual screening with CA125 as a primary test and ultrasound as a secondary test) (3) An ultrasound group (annual screening with transvaginal ultrasound). Women in the screened arms have 6 annual screens (Figure 12-1).

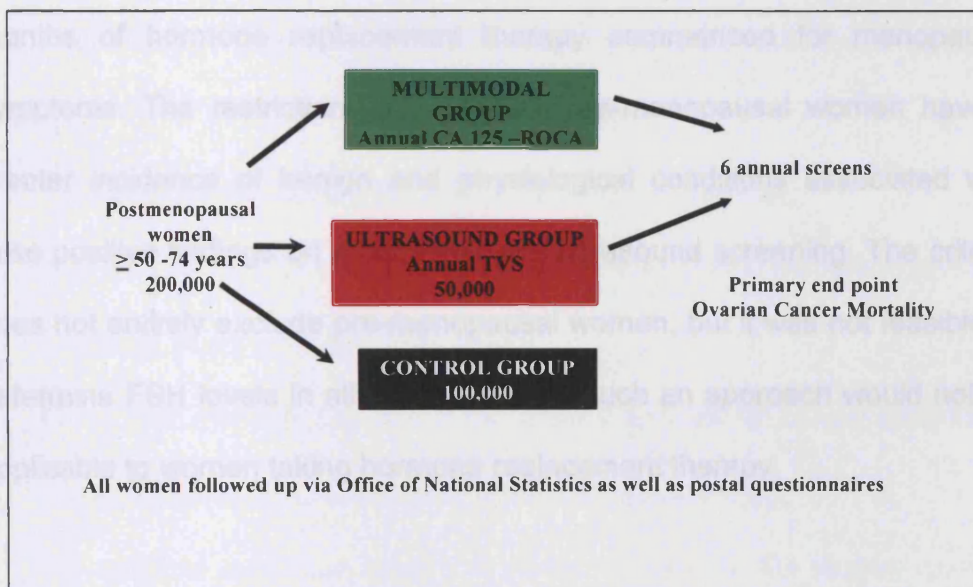


Figure 12-1: Trial design of UKCTOCS

12.4 Subjects

As this is a general population trial, the aim was to include women with the highest risk of sporadic OC.

12.4.1 Inclusion criteria

(1) Age 50-74 years: The lower cut off was chosen as primary invasive OC is uncommon below 50 years after which the incidence rises steeply¹⁶⁵.

An upper limit was fixed a

as over 74 years, mortality from other causes during the follow up is likely to be high and confound interpretation of the end point of OC mortality.

(2) Postmenopausal: This was defined as either (a) >12 months amenorrhoea following a natural menopause or hysterectomy, or (b) >12 months of hormone replacement therapy commenced for menopausal symptoms. The restriction was because pre-menopausal women have a greater incidence of benign and physiological conditions associated with false positive findings on multimodal and ultrasound screening. The criteria does not entirely exclude pre-menopausal women, but it was not feasible to determine FSH levels in all volunteers and such an approach would not be applicable to women taking hormone replacement therapy.

12.4.2 Exclusion criteria

(1) Previous ovarian malignancy

(2) History of bilateral oophorectomy:

(3) Active non-ovarian malignancy: Women who had a past history of malignancy were only eligible if (a) they had no documented persistent or recurrent disease and (b) had not received treatment for >12 months. The intention was to minimise false positive CA125 results due to advanced

stages of previously diagnosed malignancy. This exclusion did not include premalignant disease such as cervical intraepithelial neoplasia or treatment with Tamoxifen for breast cancer that was not clinically active.

(4) Increased risk of familial ovarian cancer: There are ethical difficulties in randomising high-risk women between a screened and a control group. In the UK, such women are eligible for a separate trial, the United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS). Women at high-risk were defined by the eligibility criteria for UKFOCSS. They were first degree (1^o) relatives (mother, sister or daughter) of a cancer affected member of a “high risk” family. The high-risk family was defined by one of the following criteria:

1. Two or more individuals with OC who were 1^o relatives
2. One individual with OC and 1 individual with breast cancer diagnosed under 50 years who are 1^o relatives
3. One individual with OC and 2 individuals with breast cancer diagnosed under 60 years who are connected by 1^o relationships
4. An affected individual with a mutation of one of the known ovarian cancer predisposing genes (BRCA1, BRCA2, MSH1)
5. One person with OC and three individuals with colorectal cancer with at least one case diagnosed before 50 years, all connected by 1^o relationships.
6. Affected relatives fulfilling criteria 1,2 or 3 who were related by second degree through an unaffected intervening male relative who had an affected sister.

- (5) Participation in other ovarian cancer screening trials: It should be noted that after the start of UKCTOCS, other general population OCS trials in the UK stopped recruitment and discontinued screening. These were the pilot randomised control trial, Bart's B and the ultrasound based European Randomised Control Trial Of Ovarian Cancer Screening. Both had recruited about 15,000 postmenopausal women each.

12.5 Screening regimen in the trial

The OCS strategies in UKCTOCS utilises the two screening tests – serum CA125 and/or transvaginal ultrasound (TVS) of the ovaries. The ultrasound strategy uses TVS as a first line test with repeat screening after a fixed period if an abnormality is detected on initial testing. The multimodal strategy uses serum CA125 as the primary screening modality with TVS as a second line test if levels are abnormal. The algorithms were derived from the data collected in the numerous large prospective screening studies undertaken in the 90s and discussed in the literature review.^{8 9 51 52 57} Women are screened annually for 6 years. It is anticipated that ongoing refinement of the screening algorithms will occur in the future in a manner analogous to refinement of the screening algorithms for Downs syndrome, cervical cancer and breast cancer.

12.5.1 Ultrasound Algorithm

All OC screening and diagnostic strategies incorporate TVS of the ovaries with the aim to detect the earliest morphological changes that could be linked to ovarian cancer. The main issue with use as a first line test is that a significant proportion of women require further investigations and unnecessary surgery for benign masses.

The UKCTOCS ultrasound algorithm takes into account some of the key issues raised in literature. Features include

- (1) Use of grey-scale ultrasound morphology to characterize the adnexal mass with ovarian volume playing a lesser role.
- (2) Repeat scanning of adnexal masses detected on the first screen in 6-8 weeks by a more experienced ultrasonographer
- (3) Classification of simple (unilocular) cysts less than 60mls in size as normal.¹¹¹
- (4) Possibility of conservative management of adnexal masses with less suspicious features (multicystic, multiloculated) after clinical evaluation.^{9 108}
- (5) Collection of Doppler data but no use of it in the screening algorithm as it is proven to be subjective and prone to significant interobserver variation.
- (6) Use of subjective pattern recognition as opposed to a weighted scoring system or morphological index. Data is collected on ovarian volume, outline, presence of papillary projections and cyst complexity but the final decision is driven by the clinician.

Ultrasonography is performed by about 90-100 ultrasonographers at 13 regional centres (RC). The method of choice is transvaginal ultrasonography

(TVS) but where this is not possible or acceptable to a volunteer, transabdominal ultrasonography is performed.

Annual or Level I scans are performed by ultrasonographers and Level II scans by senior ultrasonographers, gynaecologists or radiologists with particular experience in transvaginal ultrasonography. For each ovary, the ultrasonographer first decides if the ovary is visualised and the view is good (S), not visualised but a good view is obtained of the iliac vessels (N) or not visualised due to a poor view (P) resulting from bowel gas or other pelvic structures such as fibroids. In the latter case, if possible transabdominal ultrasonography is undertaken after bladder filling. Two aspects are assessed in the visualised ovary:

- (1) **Ovarian Size:** Ovarian diameter is measured in 3 dimensions. The software calculates ovarian volume using the formula for an ellipsoid ($d1 \times d2 \times d3 \times 0.523$). If it is not possible to measure the 3 dimensions of the ovary, the ovarian volume is not calculated. Instead the system calculates a mean diameter.
- (2) **Ovarian Morphology:** Ovarian echogenicity is assessed for the presence of cysts and solid areas.

Morphology is classified as

Normal: Uniform ovarian echogenicity with or without single inclusion cyst or spots of calcifications. To classify as normal the inclusion cyst must be single, less than 10mms and should not distort the outline of the ovary.

Simple cyst: Single cyst distorting the outline of the ovary, with no septae or papillations and thin wall with regular internal outline.

Complex morphology: All non-uniform ovarian echogenicity excluding single simple cyst. If there is more than one cyst with no septae or papillations and thin wall with regular internal outline, this is classified as complex morphology. Detailed description of all features - the number and size of cysts, wall regularity, presence and thickness of septae, size of papillations and echogenicity of the fluid contents are recorded. Definitions of ultrasound features and classification of cysts are as per International Ovarian Tumour Analysis (IOTA) group. ¹⁰⁴

Scans are classified based on findings in both ovaries into:

Normal: If both ovaries have either normal morphology or simple cysts <60cc or <5cms in diameter or or both ovaries are not visualised despite a good view of the iliac vessels.

Abnormal: If one or both ovaries have complex morphology or simple cysts >60cc or >5cms in diameter or ascites (vertical pool in Pouch of Douglas >10mms) is present. If any abnormality is detected on Level II scans, presence and site of colour flow Doppler is recorded.

Unsatisfactory: If one or both ovaries are not visualised due to a poor view. The exception will be those scans where one ovary is not visualised due to a poor view but the other ovary has abnormal morphology or a simple cyst >60cc or >5cms in diameter. In the latter case, the scan is classified as abnormal.

Level I screen

In UKCTOCS, women randomised into the ultrasound group have an annual TVS at their RC. Depending on the results of the scan, there are five possible courses of action (Figure 2):

- (1) Normal scan or a scan abnormality that was managed conservatively in the past and has not changed in appearance since the last annual scan: Routine screening with an annual TVS (Level 1) on the next anniversary (one year) of the date of randomisation.
- (2) Unsatisfactory scan: A repeat level I scan in 12 weeks
- (3) Abnormal scan: Level II screen in 6-8 weeks. Earlier scans are arranged where there is a high index of suspicion.

Level II screen

Depending on the results of the Level II screen, there are four possible courses of action:

- (1) Normal Scan: Routine screening with an annual TVS (Level 1) on the next anniversary (one year) of the randomisation date.
- (2) Unsatisfactory scan: Repeat Level II screen in 6 weeks with earlier screens arranged where there is a high index of suspicion.
- (3) Abnormal scan – Referral for clinical assessment.

Women who have repeat Level II screens are similarly triaged based on their findings to annual screening, clinical assessment with a view to surgery and in a minority of women, clinical management.

Scan images are centrally archived in the CC. RCs are able to request a second opinion from the senior PI at the CC with ultrasound expertise

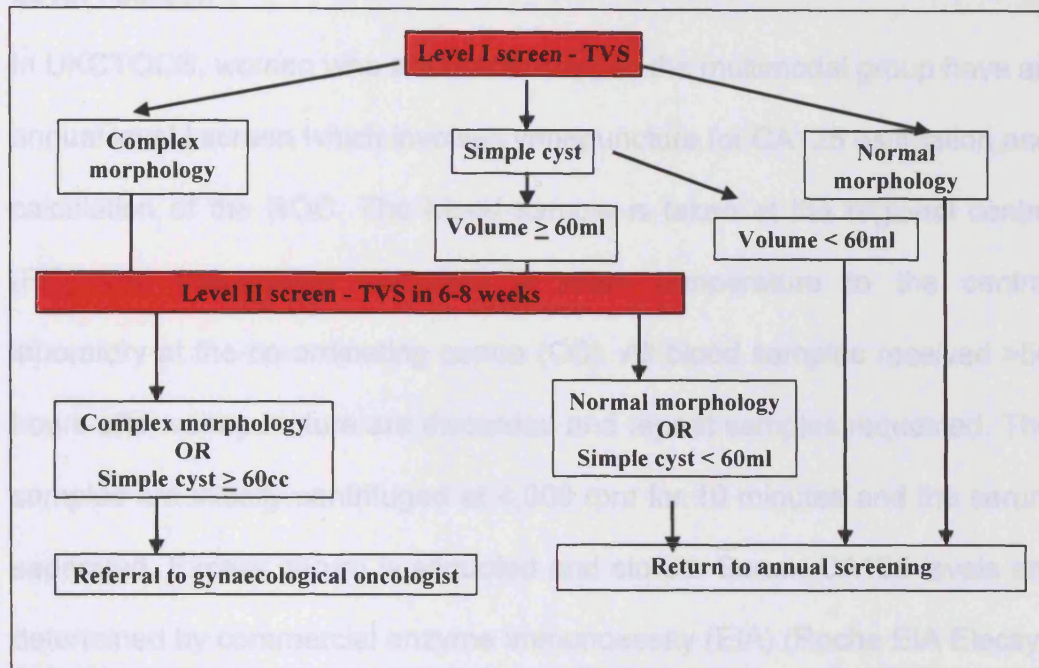


Figure 12-2: Ultrasound algorithm

12.5.2 Multimodal Algorithm

This algorithm is based on the work done previously in the Bart's A and B trials. The 'Risk Of Ovarian Cancer' (ROC) algorithm tested prospectively in the Bart's B pilot trial is used with a few logistics modifications. These include fixing the interval for a repeat blood after an intermediate ROC result at 12 weeks rather than the varied interval of 6 weeks to 6 months adopted in the pilot trail (Bart's B) and restricting number of repeat bloods to a maximum of three in any year before a woman has a TVS. Interpretation of the ultrasound findings follows the same rules as described above. Based on the results of the analysis of data from Bart's trial A, complex ovarian morphology is used for classifying scans as abnormal.

Level I screen

In UKCTOCS, women who are randomised to the multimodal group have an annual level I screen which involves venepuncture for CA125 estimation and calculation of the ROC. The blood sample is taken at the regional centre (RC) and transported overnight at room temperature to the central laboratory at the co-ordinating centre (CC). All blood samples received >56 hours after venepuncture are discarded and repeat samples requested. The samples are initially centrifuged at 4,000 rpm for 10 minutes and the serum separated. Excess serum is aliquoted and stored. Serum CA125 levels are determined by commercial enzyme immunoassay (EIA) (Roche EIA Elecsys 2010 system). The CA125 values are directly uploaded electronically into the trial database management system (DMS), which calculates the 'Risk of Ovarian Cancer'. The first ROC determination is based upon a single measurement of CA125. Subsequent ROC determinations are based upon both the absolute CA125 level and the rate of change in CA125 levels. The approach summarises in one number, the information about risk of ovarian cancer, thus simplifying the practical implementation of the screening protocol.

On the basis of the ROC, subjects are allocated to one of three groups (Figure 3):

- (1) Normal ROC: Routine screening with an annual blood test (Level 1) on the next anniversary (one year) of the randomisation date.
- (2) Intermediate ROC: Volunteers in this group are recalled for a repeat venepuncture for CA125 measurement in 12 weeks. After the repeat

CA125 the ROC is recalculated and management determined as for the initial ROC. The majority will require 1-2 repeat venepunctures to be reclassified as normal or elevated. The small proportion of subjects who remain in the intermediate group after three CA125 estimations will have a level II screen.

- (3) Elevated ROC: Women will be recalled for a level II screen in 6-8 weeks. For initial serum measurements, a CA125 level of 35 U/ml would correspond approximately to a ROC of 1 in 500.

Level II screen

Women have venepuncture for repeat CA125 assay and a transvaginal scan. The scan results are classified as detailed above. Depending on the results of the Level II screen, there are four possible courses of action:

- (1) Scan normal and the ROC normal or intermediate: Routine screening with an annual blood test (Level 1) on the next anniversary (one year) of the randomisation date.
- (2) Scan normal and the ROC elevated OR scan unsatisfactory irrespective of ROC: Repeat Level II screen in 12 weeks with earlier screens arranged where there is a high index of suspicion.
- (3) Scan abnormal irrespective of the ROC – Referral for clinical assessment with a view to surgery.
- (4) Women who have the Level II screen repeated are again triaged based on their findings to annual screening, clinical assessment with a view to surgery and in a minority of women, clinical management.

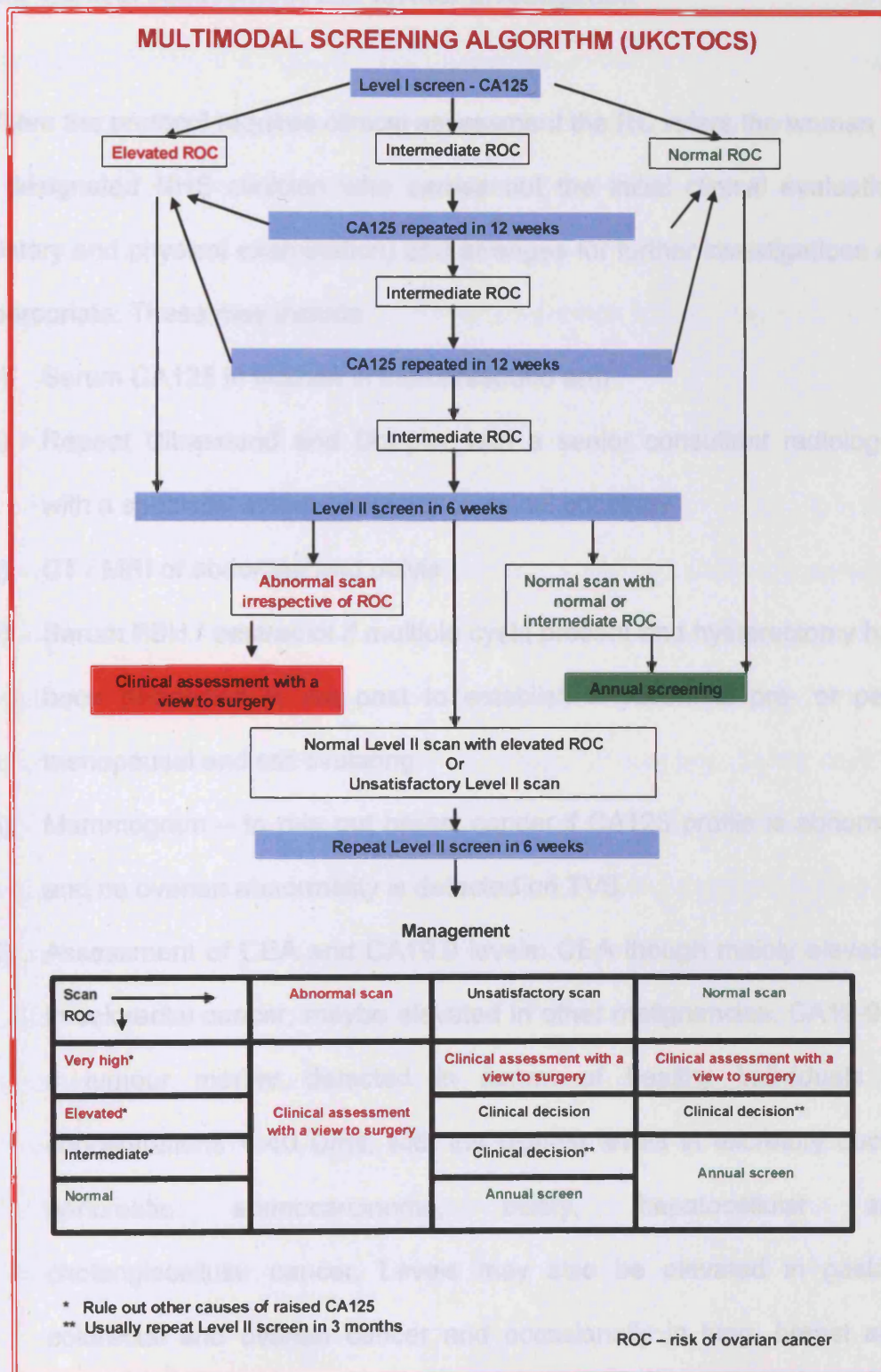


Figure 12-3: Multimodal algorithm

12.6 Clinical assessment and further investigation

Where the protocol requires clinical assessment the RC refers the woman to a designated NHS clinician who carries out the initial clinical evaluation (history and physical examination) and arranges for further investigations as appropriate. These may include

- (1) Serum CA125 in women in the ultrasound arm
- (2) Repeat Ultrasound and Doppler with a senior consultant radiologist with a specialist interest in gynaecological oncology
- (3) CT / MRI of abdomen and pelvis
- (4) Serum FSH / oestradiol if multiple cysts present and hysterectomy has been performed in the past to establish if patient is pre- or peri-menopausal and still ovulating
- (5) Mammogram – to rule out breast cancer if CA125 profile is abnormal and no ovarian abnormality is detected on TVS.
- (6) Assessment of CEA and CA19.9 levels: CEA though mainly elevated in colorectal cancer, maybe elevated in other malignancies. CA19-9 is a tumour marker detected in serum of healthy individuals at concentrations < 40 U/ml, with the highest levels in excretory ductal pancreatic adenocarcinoma, biliary, hepatocellular and cholangiocellular cancer. Levels may also be elevated in gastric, colorectal and ovarian cancer and occasionally in lung, breast and uterine cancer.

In multimodal group women, other causes of CA125 elevation need to be ruled out. In the ultrasound group, some scan features are associated with

lower risk and others with significant risk. Following consultation and clinical evaluation, if there is a high index of suspicion; women undergo surgery with a named consultant gynaecological oncologist following case discussion in the local gynaecological oncology multidisciplinary meeting. If on clinical assessment the risk of a cancer is considered to be low or if the patient refuses surgery, then conservative management with follow up is arranged.

12.7 Surgery

The nature and timing of surgical intervention is decided at the consultation between the participant and the gynaecological oncologist / gynaecologist receiving the referral. Patients undergo routine investigations that are deemed appropriate for assessment of fitness for surgery. Some centres may use pre-operative assessment scoring systems to assess possible morbidity. It is to be noted that in the ultrasound arm, women referred for surgery include a higher proportion who have had previous hysterectomy and/or endometriosis. The guidelines below represent appropriate management in the majority of cases. However, it is acknowledged that there are circumstances where they cannot be adhered to and in such situations, management depends upon the considered judgement of the clinician involved.

The primary aim of surgery is to remove both ovaries for histopathological examination. Supposedly, 'normal' looking ovaries will be removed as malignancy has been detected in such ovaries in the pilot trial (unpublished

data). However, there will be exceptions based on clinical grounds. One such occasion is where there are dense pelvic adhesions with increased risk of significant morbidity if dissection is undertaken. The clinician may opt to only remove the ovary found to have an abnormality on ultrasound and not dissect the contralateral 'normal' ovary. Hysterectomy adds to morbidity and will be avoided unless there are clear clinical indications.

The approach to surgery depends on the results of any pre-operative investigations and local surgical expertise. The primary intervention in most cases is laparoscopy with the intention of performing a laparoscopic bilateral salpingo-oophorectomy. If clinical findings at laparoscopy are suggestive of the presence of an ovarian cancer, or if laparoscopic oophorectomy is not felt to be possible because of technical difficulties, a laparotomy is undertaken.

Laparoscopy - The procedure is carried out using the surgeon's preferred technique. A thorough inspection of the whole of the abdominal cavity is performed before aspirating any free fluid that is present and/or taking peritoneal washings. If technically possible and in the absence of any features suggestive of ovarian cancer, a bilateral salpingo-oophorectomy is performed. Care is taken to ensure removal of the entire ovary on each side. The operative specimen is placed inside a bag prior to removal from the abdominal cavity in order to minimise the risk of spillage of cyst contents if cyst rupture occurs during this process. Aspiration of ovarian cysts should be avoided since a stage 1A cancer may be unwittingly be converted to a stage 1C. When a histopathological diagnosis of ovarian cancer is made

following a laparoscopic bilateral salpingo-oophorectomy a formal staging laparotomy is performed within 2 weeks of initial surgery.

Laparotomy - If there is a clinical suspicion of ovarian cancer the surgeon carries out the laparotomy according to their usual practice in order to stage the disease and remove all macroscopic disease where possible.

Details of all surgical procedures undertaken to investigate screening results is collected including the operative procedure, the surgical findings, the histopathological findings, details of the postoperative course and any complications.

12.8 Conservative management

A large number of asymptomatic benign adnexal masses are detected especially in the ultrasound arm of the trial. In women who have had previous hysterectomy, there is an increased chance of adhesions and peritoneal pseudo cysts being reported as 'multilocular adnexal cysts'. Following clinical assessment, investigation and discussion with the woman, if the plan is made to avoid surgery and manage conservatively, then women are followed by a repeat transvaginal scan and possibly a serum CA125 assessment in three months. They are returned to annual screening if the findings are unchanged at review. At subsequent screens, no action is taken if there is no change in the size or character of the adnexal lesion detected.

12.9 Follow-up

The primary end points of the trial are ovarian cancer diagnosis and mortality. In a previous OCS trial, the National Health Service Central Register ascertainment in 1999 was found to be incomplete and direct follow-up provided additional information.¹⁶⁶ Hence trial follow up includes postal questionnaire and flagging via the Office of National Statistics.

All volunteers are sent a postal questionnaire 3.5 and 7 years from the randomisation date. The questionnaire asks for details of any gynaecological procedures, cancer diagnosis or serious illness since recruitment and contact details of the clinician who treated the condition. Further details of these procedures are then be obtained as appropriate. In order to assess contamination, the follow up questionnaire also asks women in the control group if they have undergone a pelvic ultrasound scan or CA125 test since randomisation and if so the reason for the test.

All volunteers were asked for consent for their contact details to be sent to the Office of National Statistics (ONS) for England and Wales or the Cancer Registry of Northern Ireland depending upon their place of residence. The computerised entry for each subject at the registry is 'flagged' to prompt notification to the CC of deaths and all new cancer diagnoses in the study population.

12.10 Confirmation of outcome

Where any method of follow up raises the possibility of ovarian cancer further information is requested from the GP and/or hospital where treatment is provided. In addition, to ensure that all deaths from ovarian cancer are documented, a copy of the death certificate is requested for all study participants who die during follow up. In addition, survival at end of study for participants with a confirmed diagnosis of ovarian cancer will initially be confirmed from the final postal questionnaire. For participants who do not return the questionnaire further inquiries will be made via the GP to establish their status. An independent outcomes committee reviews each case and confirms diagnosis and mortality due to OC.

12.11 Sample Size

The proposed sample size of 200,000 is based on primary comparison between the control group and the two screened groups combined with the primary outcome measure mortality from ovarian cancer. There are approximately 37 deaths from ovarian cancer per 100,000 women aged 50-74 per year. Assuming an attrition rate of 4% per year (75% of patients followed up for the full 7 year period) gives a mean of 6 person years of observation for each patient randomised, and thus an expected number of deaths from ovarian cancer in the control group of 222 per 100,000 women randomised. The event of interest, death from ovarian cancer, is rare and so it is assumed that the observed number of deaths in each group follows a

Poisson distribution. Under these assumptions, a total sample size of 200,000 (100,000 controls, 50,000 in each screening group) would give 80% power at the (two-sided) 5% significance level to detect a reduction in mortality due to screening of 25% (167 deaths in the screening groups), and over 90% power to detect a reduction of 30% (155 deaths in the screening groups). Comparisons between the multimodal and control groups and between the ultrasound and control groups are also of primary interest. With the above assumptions, the trial will have 80% power at the (two-sided) 5% significance level to detect a 30% reduction in mortality compared to the control group and 63% power to detect a 25% reduction. It is important to note that if one comparison is significant and the other is not, this result does not necessarily imply that one method is significantly better than the other. Only the direct comparison between the two methods will address this issue. The trial has at least 70% power to detect a difference in OC mortality between the two screening arms of 30% or more. However, if as anticipated the difference in OC mortality between the two screened groups is modest then this study will have limited power to detect such differences e.g. 35% power to detect a difference of the order of 20%. The choice of screening strategy will then be based on other outcome measures such as sensitivity, positive predictive value, morbidity, quality of life, and health economics.

At the end of recruitment, the original power calculation was reviewed. Deaths in any particular year from ovarian cancer occur largely in women diagnosed with the disease in the preceding 2-3 years. Based on eligibility criteria women with ovarian cancer cannot join the trial. Hence one of the

concerns was that this will result in a reduction in the number of deaths from ovarian cancer in the early years of the trial when compared to the anticipated numbers adopted in the original power calculations, which did not factor in this effect. This could have two possible effects

- (1) Decline in the number of control group deaths, particularly during the initial years, resulting in a reduction of anticipated events (deaths from ovarian cancer) at the end of the 7 years follow up.
- (2) A reduction in mortality differences between the screen and control groups, if the primary analysis is performed 1 year after the last screen. As women usually die about 2-3 years after initial diagnosis, a sufficient period of time may not have passed to demonstrate the efficacy of screening.

Hence, the expected number of control group deaths was recalculated with more precision taking into consideration several factors.

- (1) Firstly, the mortality rate for ovarian cancer used initially was an average value that covered the entire age range. However as the age distribution of the recruited 202,638 women is now known, age-group specific mortality rates were used.
- (2) Linked to the above, it was now possible to calculate the numbers of women in each respective age group as the trial progresses, reflecting the increasing age of the women.
- (3) The original calculations employed an average 4% annual attrition rate for the trial. This is very conservative because women remain flagged with the ONS even if they have withdrawn from participating in the

screening. Death and cancer registration information continues to be available until censorship. All women effectively contribute to the trial (at least with regard to this main outcome measure) unless they actually die, whereupon they are of course then unable to die of ovarian cancer. So in place of an attrition factor one instead needs to adjust for a mortality factor of deaths from other causes that reduces the effective population at risk from ovarian cancer.

- (4) Finally, it is necessary to account for the reduction in deaths due to the eligibility criteria, as discussed.

Table 12-1 Power values for tests of control versus screen combined is for the test of the control group mortality versus the screen groups combined, and has power values based on the 7, 8 and 9 year control deaths totals compared against a range of potential mortality reductions from screening (15-50%). If the true mortality reduction is of the order of 30% then a power value of 0.888 suggests that 7 seven years might be sufficient.

Table 12-1 Power values for tests of control versus screen combined

Mortality reduction	7 years total		8 years total		9 years total	
	C deaths: 193.1		C deaths: 231.8		C deaths: 271.4	
	S deaths	Power	S deaths	Power	S deaths	Power
15%	164.1	0.334	197	0.388	230.7	0.443
20%	154.5	0.543	185.44	0.62	217.1	0.689
25%	144.8	0.745	173.9	0.818	203.6	0.873
30%	135.2	0.888	162.3	0.936	190	0.964
40%	115.9	0.991	139.1	0.997	162.8	0.999
50%	96.6	1	115.9	1	135.7	1

C=control group; S= Screen groups combined

In Table 12-2 the power values for comparison between the control group and an individual screening arm is presented. Inevitably with a reduced sample size (approx. 50,000 compared to 100,000) this means reduced power values. The 7-year value for a 30% reduction of 0.722 may not be considered high enough and even possibly the 8-year value of 0.795 either. Given that this comparison is important to assess whether individually each of the arms shows an effect than the arms combined, these results suggest that at least 9 years from randomisation maybe appropriate.

Table 12-2: Power values for tests of control versus individual screen

Mortality reduction	7 years total		8 years total		9 years total	
	C deaths: 193.1		C deaths: 231.8		C deaths: 271.4	
	S deaths	Power	S deaths	Power	S deaths	Power
15%	82.1	0.241	98.5	0.278	115.3	0.317
20%	77.2	0.391	92.7	0.453	108.6	0.511
25%	72.4	0.562	86.9	0.638	101.8	0.704
30%	67.6	0.722	81.1	0.795	95.0	0.852
40%	57.9	0.926	69.5	0.961	81.4	0.980
50%	48.3	0.989	58.0	0.996	67.9	0.999

C=control group; S= Individual screen groups

The plan is to screen women in the study arms for 6 years and then to build in the possibility of extending follow up for each woman in the cohort from 7 to 9 years from date of randomisation. Recruitment was completed in September 2005 and in Oct 2010, as initially envisaged screening will be complete. Follow up for each woman will continue to the end of 9 years from date of randomisation such that the last woman randomised is censored in October 2014. Depending on the mortality reduction achieved in either of the

screen arms, the study may reveal a mortality difference from as early as 2011.

12.12 Secondary objectives

12.12.1 Performance characteristics of the two screening strategies

Sensitivity, specificity and positive predictive value will be estimated for each screen (Table 3). The screening strategy includes the screening tests, the screening algorithms, clinical evaluation and culminates in either surgery or a return to annual screening. The primary analysis of performance characteristics will therefore be based on women who have surgery in the trial as a result of screen positive findings. The outcome measure for this primary analysis will be primary ovarian cancer. Sensitivity will be calculated in the standard fashion as the ratio of screen detected cases to all cases found through some interval usually a year after a screen as well as from date of randomisation. Performance characteristics for detection of primary invasive epithelial ovarian cancer will be calculated separately.

Table 12-3: Performance characteristics of the screening strategies

Surgery in the trial following screen positive findings	Primary ovarian cancer*	Primary ovarian cancer* not diagnosed	Performance characteristics
Yes	a	b*	Sensitivity = $a/(a+c)$ Specificity = $d/(c+d)$ PPV = $a/(a+b)$
No	c	d	

*includes all malignant ovarian neoplasms

12.12.2 Physical morbidity resulting from surgical intervention attributable to screening

The safety risk is not associated with the screening procedures themselves but with the surgical investigation of abnormal screen results by laparoscopy or laparotomy. All serious adverse reactions that are possibly trial related are documented. They are broadly defined as any untoward deviations from baseline health that are possibly related to recruitment, screening and surgery within UKCTOCS. Suspected serious adverse reactions (SSAR) are known complications of the procedures undertaken in the trial and are listed in Appendix 1. An Adverse Reaction is a SUSAR (Suspected Unexpected Serious Adverse Reactions) if its nature and/or severity is not consistent with known complications of the surgical or screening procedure or if it is fatal or life-threatening. An independent Data Monitoring and Ethics Committee (DMEC) examine all SUSARs and complications. The SUSARs are also reported annually to the Multicentre Research Ethics Committee that monitors the trial.

The excess surgical morbidity and mortality in the trial will be calculated on the assumption that all operations for cancer and 25% of operations for false positive results would ultimately have been required regardless of the trial. Data obtained through the follow up questionnaire on the incidence of gynaecological surgery for benign indications in the control arm will help refine this calculation.

12.12.3 Feasibility of screening, as reflected by compliance rates with annual screening

There will inevitably be less than complete compliance with annual screening. The rate of compliance is an important end point of the study as it has implications for the feasibility of introducing a national screening programme. In the initial randomised control trial 99.3% and 96.8% of the volunteers who underwent an initial screen following randomisation, attended for their 2nd and 3rd annual screens respectively.⁸ The proposed trial will involve 6 screens but it is reasonable to anticipate an overall compliance with screening in excess of 75%. Our estimates allow for an annual attrition rate of 4%, which translates to an overall compliance with 6 annual screens of 78%.

12.12.4 Psychological consequences of screening

The overall aim of the quality of life study is to assess the psychosocial factors affecting behavioural and emotional responses to OC screening. It is coordinated by the Psychosocial Oncology Group, Brighton and Sussex Medical School.

12.12.5 Resource implications of screening and the resulting interventions

The trial is powered for primary clinical end-points and consequently the analysis for the economic end-points is within these constraints. Statistical analysis will however be undertaken on the calculated cost-effectiveness ratios that are crucial to the trial. The economic evaluation will include both a within trial analysis and a modelling analysis. The analysis will be undertaken by the group at the Department of Social Policy, London School of Economics, London.

12.13 Serum bank

Women have provided written consent to use of their serum samples for ethically approved secondary studies, the focus of which is the early detection and treatment of disease. A baseline serum sample has been stored for all participants and serial samples are being stored in the 50,000 women in the multimodal group who have annual screening.

12.14 Study organisation

The study was designed and is coordinated by the Department of Gynaecological Oncology, located initially at Queen Mary University London and since April 2004 at University College London (UCL). It is conducted through 13 regional trial centres (RCs) in England, Wales, and Northern

Ireland which are mainly located in NHS Trusts (Figure 4). UCL are legal sponsors for the trial.

UKCTOCS – TRIAL DESIGN AND ORGANISATION

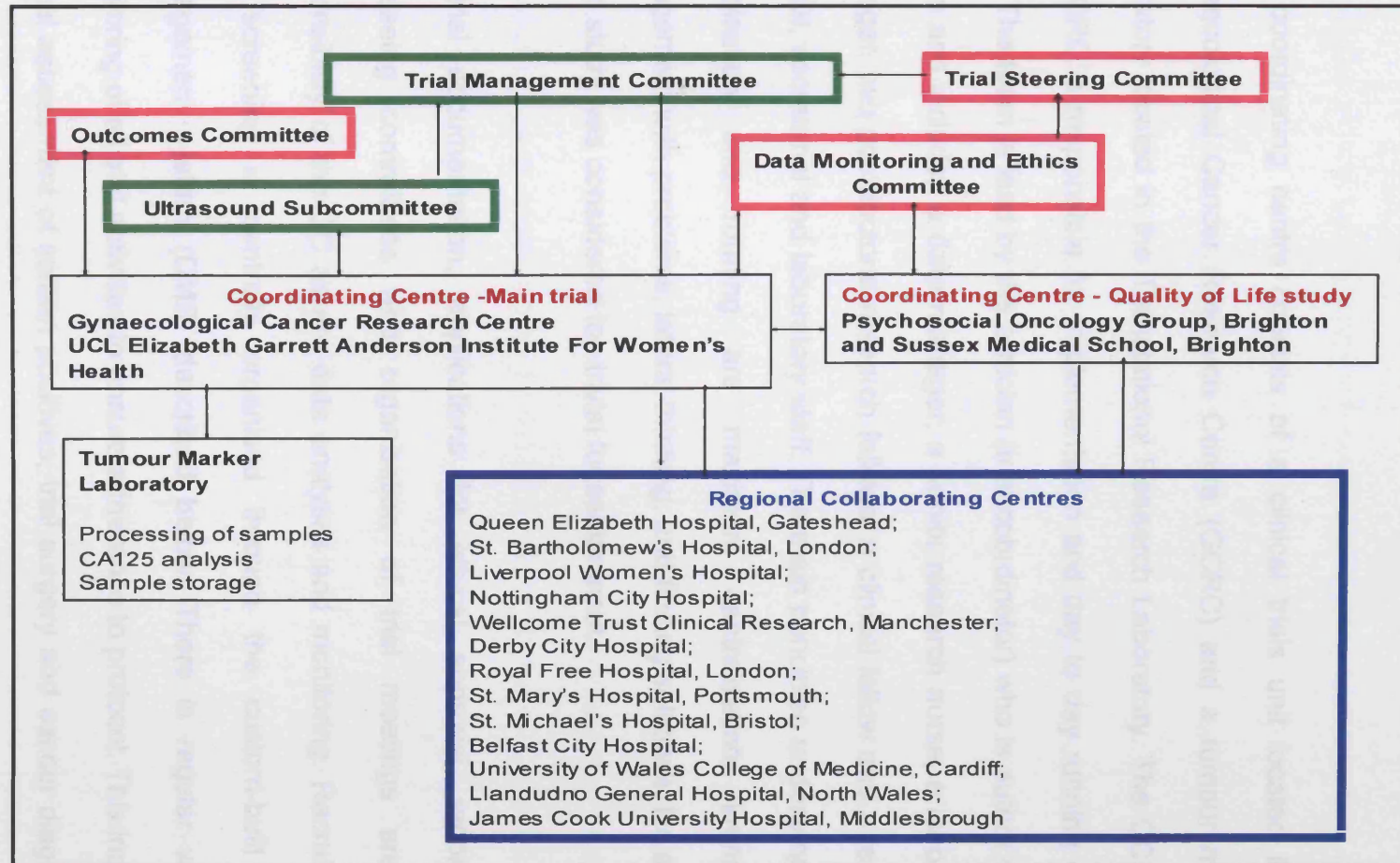


Figure 12-4: UKCTOCS Organisation

12.14.1 Coordinating Centre (CC) Team

The coordinating centre consists of a clinical trials unit located in the Gynaecological Cancer Research Centre (GCRC) and a tumour marker laboratory located in the Translational Research Laboratory. The CC team at GCRC is responsible for implementation and day to day running of the trial. The team is lead by the clinician (trial coordinator) who is author of this thesis and includes a data manager, a senior research nurse, a laboratory manager, two postdoctoral research fellows, a clinical fellow and a team of clerical, secretarial and laboratory staff. The main principles underlying trial organisation and running are maximum centralisation, immediate engagement with problems, lateral thinking, and finding solutions. No aspect of the study was considered too trivial for senior input.

All trial documentation, applications for ethical approval, reports to overseeing committees and organisation of trial meetings are the responsibility of the CC as are data analyses and monitoring. Recruitment and screening is centrally organised through the custom-built data management system (DMS) described below. There is regular weekly monitoring of all trial activities to ensure adherence to protocol. This includes clinical assessment of screen positives, trial surgery and cancer diagnosis. This is done by a series of database checks (fail-safe procedures), close

liaison with the RC teams and direct communication with the trial participants. Follow up is entirely the responsibility of the CC team.

12.14.2 Regional Centres

At the RCs, there is a dedicated trial team consisting of a research nurse, phlebotomist, clerk, and ultrasonographers led by a consultant clinician (Lead Researcher). Recruitment of the trial participants and performance of the screening tests are the responsibility of the RC. The team arranges clinical evaluation of women confirmed to have abnormalities on Level 2 screens and arranges for referral to the appropriate NHS clinic if surgery is appropriate. Copies of all documentation are forward to the CC for data entry expect for ultrasound results which are entered live over the web. There are regular meetings of all the RC teams at the CC once a year. Regular visits of RCs by CC staff are undertaken.

12.14.3 Data Management System (DMS)

The trial DMS is based on an earlier prototype which was extensively revised and further developed by the author working with the commercial company Xchanging. It includes a web browser and high security encryption which allows live data entry from the RCs and the laboratory and makes it

possible to run the trial centrally from the CC. All trial clinics (recruitment, phlebotomy, and ultrasound) at the RCs are set up on the DMS.

The main functions of the DMS are invitation of women whose details are uploaded from electronic files provided by participating PCTs; scheduling of recruitment appointments at the appropriate RCs when acceptances are logged on the system; automated checking for a complete dataset following scanning of recruitment datasheets; randomisation of eligible women; scheduling of screening appointments, classification of serum CA125 and ultrasound results, assignment of follow up as per screening algorithms with scheduling into appropriate clinics.

Automated letter printing includes invitation letters to join study, appointment letters to all trial clinics, requests for further data when minimum dataset is incomplete; confirmation of randomisation with notification of individual general practitioners, screen results and follow-up plan. There are numerous failsafe measures set up such as automatic prompts for overdue screen results.

The functionality incorporates download of contact details to the Office of National Statistics (ONS) for flagging; upload of cancer registrations files from ONS and weekly downloads of data to Quality of Life Study team so that screening events can be followed up. The DMS maintains an interface

with the laboratory which makes possible tracking of serum samples from RC phlebotomy clinics via processing in the central laboratory to storage in the biorepository. For women in the multimodal group, requests for CA125 assays of appropriate samples are generated and the results are directly uploaded from the CA125 analyser.

Using the web browser function, staff at the RCs are able to log acceptance of invitations, edit volunteer contact details and withdraw volunteers; maintain trial clinics (cancel clinics over holidays and reschedule appointments) and enter data (attendance at clinics, date/time blood sample taken, details of ultrasound scan performed).

The security of the DMS is ensured by server & client certificates; username /passwords stored within SQL and on Win2K server domain. The DMS is upgraded on a regular basis to accommodate protocol development.

12.14.4 Serum bank

Serum samples are shipped overnight in the Grienger gel tubes and processed the next day in the central UKCTOCS laboratory. A novel semi automated system aliquots serum in 500 micro litre straws which are then heat sealed and bar coded and stored in special containers in liquid nitrogen tanks. The tanks once filled and shipped off site to a cryonic biorepository.



Figure 12-5: Novel storage solutions for the UKCTOCS serum bank

12.14.5 Committee Structure

There are two committees comprised of UKCTOCS researchers whose focus is implementation. Three mainly external committees oversee progress, monitor safety, of volunteers and data, and confirm outcomes (Figure 12-4).

Trial Management Committee (TMC)

This committee oversees the implementation of the trial. It consists of the principle investigators, trial coordinators of both the main trial and the Quality of Life study, three RC lead researchers and the CC data manager, statistician and research fellows. It meets formally twice a year with frequent email discussions as issues arise.

Ultrasound Sub-committee

The committee consists of UKCTOCS researchers with a particular expertise in ultrasound or its delivery. The main purpose of the committee is to oversee the ultrasound arm of the trial and to monitor adherence to protocol, develop quality assurance, advice on the logistics of ultrasound delivery, training of staff and solutions for sustaining a high standard of scanning in the trial.

Trial Steering Committee (TSC)

The trial steering committee provides overall supervision and ensures that the trial is conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice. In its deliberations, the rights and well-being of the trial participants are the most important consideration. Its role includes monitoring progress and adherence to protocol. The TSC evaluates reports from DMEC based on efficacy and safety analyses and determines what constitutes the minimal important difference for the futility analysis. UKCTOCS TSC has five independent members including the chair. Three observers from the funding bodies attend the meetings.

Data Monitoring and Ethics Committee (DMEC)

The safety committee includes four experts (gynaecological oncologists, epidemiologist and senior scientist) not directly affiliated with UKCTOCS. It monitors the trial and reports to the TSC. The safety committee's primary

responsibility is to safeguard the well-being of patients enrolled in the trial. It reviews all adverse reactions/complications and complaints. It monitors performance of RCs, recruitment, compliance with screening, logistic issues with delivery of the screening, performance characteristics of the screening strategies and supports/makes recommendations for protocol changes including recommendations for early dissemination of results. The trial coordinator and lead statistician report to DMEC which reviews the trial every 6-12 months.

Outcomes Committee

The committee consists of a independent gynaecological oncology pathologist, gynaecological oncologist and an epidemiologist. The main purpose of the committee is to review each ovarian cancer case in the trial to confirm the diagnosis and/or death is due to ovarian cancer.

12.15 Discussion

The UKCTOCS trial represents a major commitment of resources from the Medical Research Council and the Department of Health, UK. The design is a three arm randomised controlled trial that allows for direct comparison of the control group with the two screening groups combined as well as with each of the screening groups alone. The sample size has been chosen to ensure a valid scientific assessment of impact of the screening strategies on

ovarian cancer mortality while comprehensively addressing the questions of performance characteristics of the strategies, cost, physical and psychological morbidity and compliance.

An RCT of OCS is also underway as part of the PLCO trial¹⁵⁸. The main differences are that in the latter only the primary screen (combined serum CA125 and ultrasound) is under the purview of the trial. Women with abnormalities detected are then referred to their personal physicians. In UKCTOCS, there is a well-defined screening strategy which includes screening algorithms with first and second lines tests, clinical evaluation within the trial for women requiring assessment and finally surgery. This is similar to the NHS cervical screening programme in the UK. 78,237 women aged 55-74 were recruited into PLCO with 28,816 undergoing prevalence screen.¹³³ Overall each woman will have 6 screens and follow up for 13 years. In UKCTOCS, 100,000 women will undergo 6 annual screens and follow up will be for 7-9 years from randomisation so that there is no dilution of the screening effect.

The results of UKCTOCS will provide essential information about the benefits and adverse effects of OC screening. If the study does not reveal a reduction in OC mortality attributable to screening, then it will provide an evidence base for discouraging the introduction of population screening. If the study reveals a mortality benefit from screening an informed debate will

be possible about the wisdom or otherwise of introducing an OC screening programme in clinical practice and about the optimal screening strategy. The debate will need to consider the size of the mortality benefit, physical and psychological morbidity, compliance, cost, and logistic issues related to delivery of the screening strategies. Without evidence from a well-designed trial such a debate will not be possible.

The trial provides a great resource as the serum bank amassed for the duration of the trial may prove invaluable for discovery of novel tumour markers for pre-clinical detection of ovarian cancer.

13 UKCTOCS - RECRUITMENT OF 200,000 WOMEN

13.1 Introduction

Randomised controlled trials (RCTs) are widely accepted as the gold standard for evaluating healthcare interventions. However, less than one third (31%) of UK Medical Research Council (MRC) and NHS Health Technology Assessment (HTA) Programme funded multicentre RCTs recruiting between 1994 and 2002 achieved their original recruitment target.¹⁶⁷ This has significant implications in lost opportunity costs for trials that fail to complete and cost, inconvenience and loss of statistical power for completed trials¹⁶⁸. In this respect, UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS, www.ukctocs.org) is a success story. Funded jointly by MRC, NHS R&D and Cancer Research UK (CR-UK), it completed recruitment in September 2005 to become the world's largest randomised control trial. This chapter describes the challenges of recruiting 200,000 women together with the innovative solutions that made it possible.

13.2 Methods

As described in the previous chapter, the design of UKCTOCS involves recruitment of 200,000 women randomised to annual screening with serum CA 125 (50,000); transvaginal ultrasound (50,000) or no intervention (100,000). Screening is for 6 years and all women are followed up by postal questionnaire and through flagging via the Office of National Statistics.

13.2.1 Ethics

Ethical approval was obtained from the Multicentre Research Ethics Committees (North West) and site specific approval from the Local Regional Ethics Committees for each of the participating Regional Centres (RCs) and their associated Primary Care Trusts (PCTs). Approval was also obtained from the Caldicott Guardians of each of the participating PCTs. Written consent was obtained from all women who were recruited.

13.2.2 Coordinating Centre (CC)

Invitation, recruitment and randomisation was centrally organised through the data management system (DMS). The CC team ensured that adequate numbers of women were invited in a timely manner such that appointments at the recruitment clinics at the RCs were booked. Recruitment rates were closely monitored and close liaison was maintained with the RC teams.

13.2.3 Regional centres (RCs)

12 regional centres were set up with a target recruitment of 16,667 women over the course of 3 years. The number of centres was decided on cost efficiency and optimal logistic feasibility. Key factors determining the latter were the number of women who could be recruited in a week by a full time research nurse; the maximum number of ultrasound scans that could be performed in a year by a full time ultrasonographer using one ultrasound

machine; the number of screen abnormalities and surgical referrals a centre could manage without significant impact on the routine NHS work; and the space requirements for running such a trial. All RCs identified a designated trial area which included a waiting room and separate rooms for interviews and phlebotomy.

13.2.4 Database management system (DMS)

The customised database management system (DMS) has been described in the previous chapter. Key features supporting recruitment and randomisation are automated processes for invitation, scheduling of appointments to recruitment clinics at RCs, checking of eligibility following scanning of the recruitment datasheets into the system, randomisation, generation of requests when data incomplete and printing of letters to participants and their GPs. A web browser and high security encryption enables all trial staff whether located at the CC, RC or the central laboratory to enter and see live data at all times. This feature supports rescheduling of appointments whether women ring the CC or the RC.

In addition, specialised software was commissioned from the NHS so that women aged between 50 and 74 years could be randomly chosen from the age/sex registers held by their PCT and their contact details, date of birth, NHS number, and GP details could then be downloaded to the CC as an electronic file. The software ensured that the women were then flagged on

the PCT register such that their details were not included in future downloads.

13.2.5 Invitation

Electronic files with details of all General Practitioners (GPs) working in participating PCTs were uploaded into the trial DMS. A letter was sent to each of them with information about the study.

Electronic files containing details of 2,000 – 10,000 women were requested on a regular basis from each of the participating PCTs by the CC. These files were uploaded into the trial DMS. Women were then sent personal invitations to join the study along with a brochure outlining the trial objectives, design and inclusion/ exclusion criteria. Women were asked to return the tear away slip (Figure 13-1) using the freepost address provided. The slip had each individual's study number and details pre-printed. This maximised efficiency and minimised errors when the returned information was logged on to the DMS by RC staff via the web browser.

13.2.6 Recruitment

The recruitment clinic profile was set up on the DMS for all RCs. The DMS every night automatically scheduled recruitment clinic appointments at the appropriate centre for women who accepted invitations. Recruitment appointment letters were printed and sent to the women along with a

WE WOULD BE VERY GRATEFUL IF YOU WOULD RETURN THIS SLIP	
Ref: {Volunteer Reference No}	
I {volunteer name} of {volunteer address}	
1. I would like to take part in the UKCTOCS study.	<input type="checkbox"/>
2. I cannot take part because	
More than one person in my family has ovarian cancer	<input type="checkbox"/>
I am currently being treated for cancer	<input type="checkbox"/>
I had ovarian cancer	<input type="checkbox"/>
I had both my ovaries removed	<input type="checkbox"/>
I am still having periods	<input type="checkbox"/>
I am taking part in another ovarian cancer screening trial	<input type="checkbox"/>
3. I do not wish to participate in this study	<input type="checkbox"/>
Signed.....	
Date.....	

Figure 13-1: Reply slip returned by women

detailed trial information sheet from the CC. Appointments were made 6 weeks in advance to allow adequate time for rescheduling. Women were able to ring either the RC or the CC to change appointments.

At the recruitment appointment, women completed a one page recruitment questionnaire, which included information regarding eligibility. Those who were willing to participate in the psychosocial study were given a set of baseline quality of life questionnaires to complete and return to the researchers in a pre-paid envelope. Written consent included separate consents for the main trial and the psychosocial study and a data protection form. All volunteers provided a baseline serum sample that was sent over night to the central laboratory at the CC for storage (Figure 13-2). Attendance at the recruitment clinic was recorded on the DMS in real time over the web browser.

UKCTOCS –RECRUITMENT AND RANDOMISATION

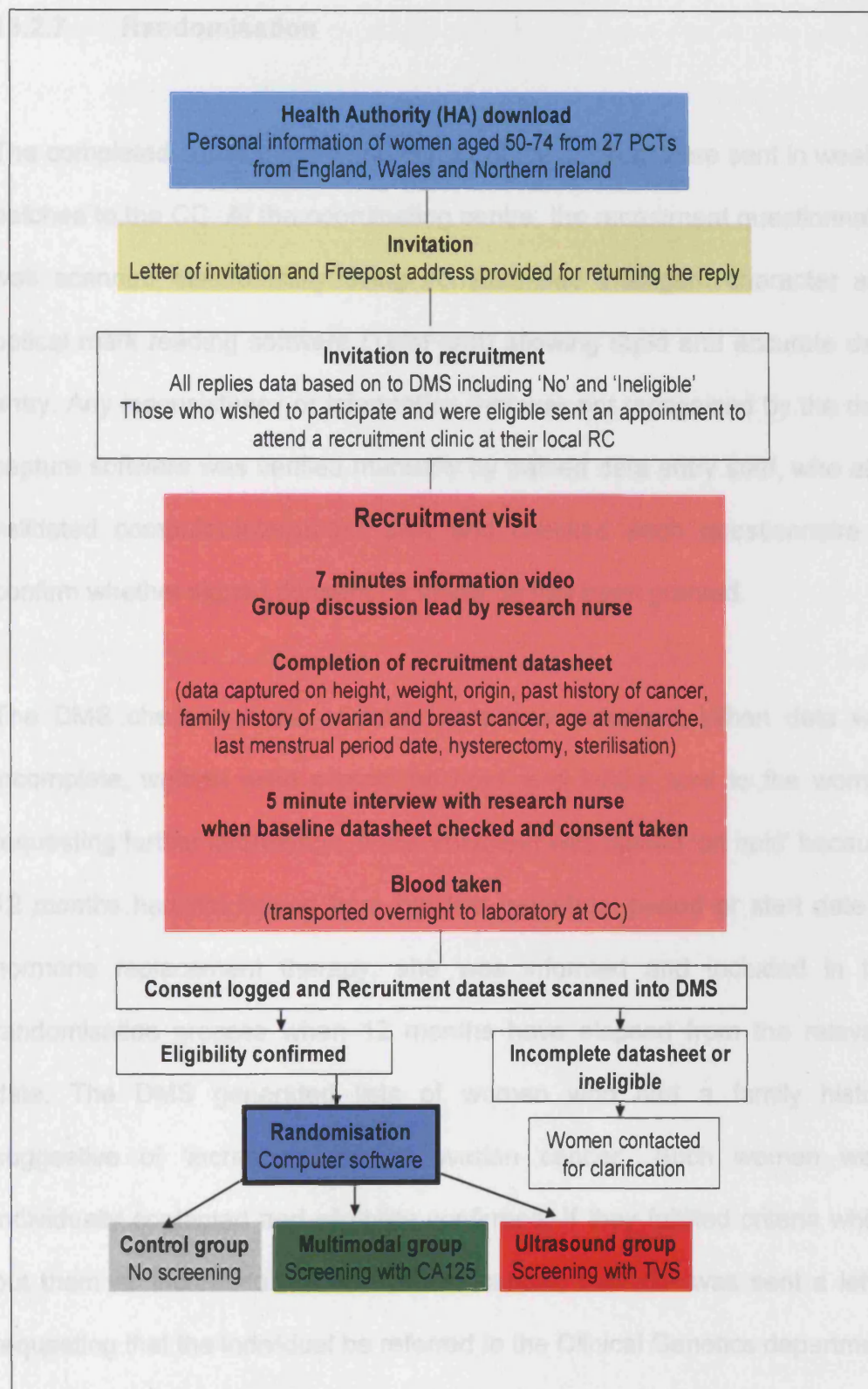


Figure 13-2: UKCTOCS Recruitment flow chart

13.2.7 Randomisation

The completed questionnaire and copies of the consent were sent in weekly batches to the CC. At the coordinating centre, the recruitment questionnaire was scanned electronically using computerised intelligent character and optical mark reading software (TeleForm) allowing rapid and accurate data entry. Any inconsistency or information that was not recognised by the data capture software was verified manually by trained data entry staff, who also validated computer-interpreted data and checked each questionnaire to confirm whether signed consent for follow up has been granted.

The DMS checked if the eligibility data was complete. When data was incomplete, women were placed 'on hold' and letters sent to the women requesting further information. If the Volunteer was placed 'on hold' because 12 months had not lapsed from her last menstrual period or start date of hormone replacement therapy, she was informed and included in the randomisation process when 12 months have elapsed from the relevant date. The DMS generated lists of women who had a family history suggestive of 'increased risk of ovarian cancer'. Such women were individually contacted and eligibility confirmed. If they fulfilled criteria which put them at 'increased risk' for familial cancer, their GP was sent a letter requesting that the individual be referred to the Clinical Genetics department for risk assessment.

Once the DMS confirmed eligibility, participants were randomised to the control group, multimodal (CA125) group, or ultrasound group.

Randomisation was carried out as follows:

1. The DMS allocated a set of 32 random numbers to each RC
2. The lowest 8 were allocated to the M-group, the next 8 to the U-group and the remaining 16 to the C-group.
3. Each successive Volunteer within the RC was randomly allocated one of the random numbers and hence randomised into a group
4. When all 32 random numbers had been used up a further set of 32 were generated.

The actual randomisation was accomplished by using the Visual Basic Randomisation statement and the Rnd function. Once the woman had been randomised, the date of randomisation was stored on the database. The system then automatically printed letters to the woman and her GP confirming eligibility and randomisation status.

13.2.8 Complaints

All complaints were lodged and monitored centrally. A designated CC person wrote to each woman directly after investigating the issues raised. All suggestions by the women were explored and trial logistics amended when appropriate and possible.

13.3 Results

Prior to the start of the trial, 12 Gynaecological Oncology departments expressed interest in participating. However, in the set up phase, the Scottish centres and two of the English centres were unable to secure support from their respective Trust management boards. Key issues were space and retirement of the local principle investigator. Various possibilities were explored and after much negotiation, new trial centres were finalised at Cardiff, North Wales, Manchester, and Derby (Figure 13-3). In 2003, a 13th centre became possible through a combination of circumstances: the determination of the investigators to build a safety net, the particular centre's expertise in OC screening acquired through participation in a previous trial and Cancer Research UK's willingness to support one further centre with additional funds. No overall recruitment target was set for this centre. Instead, it was agreed that this centre should have the same target monthly recruitment rate as the other centres.

UKCTOCS –RECRUITMENT AND RANDOMISATION

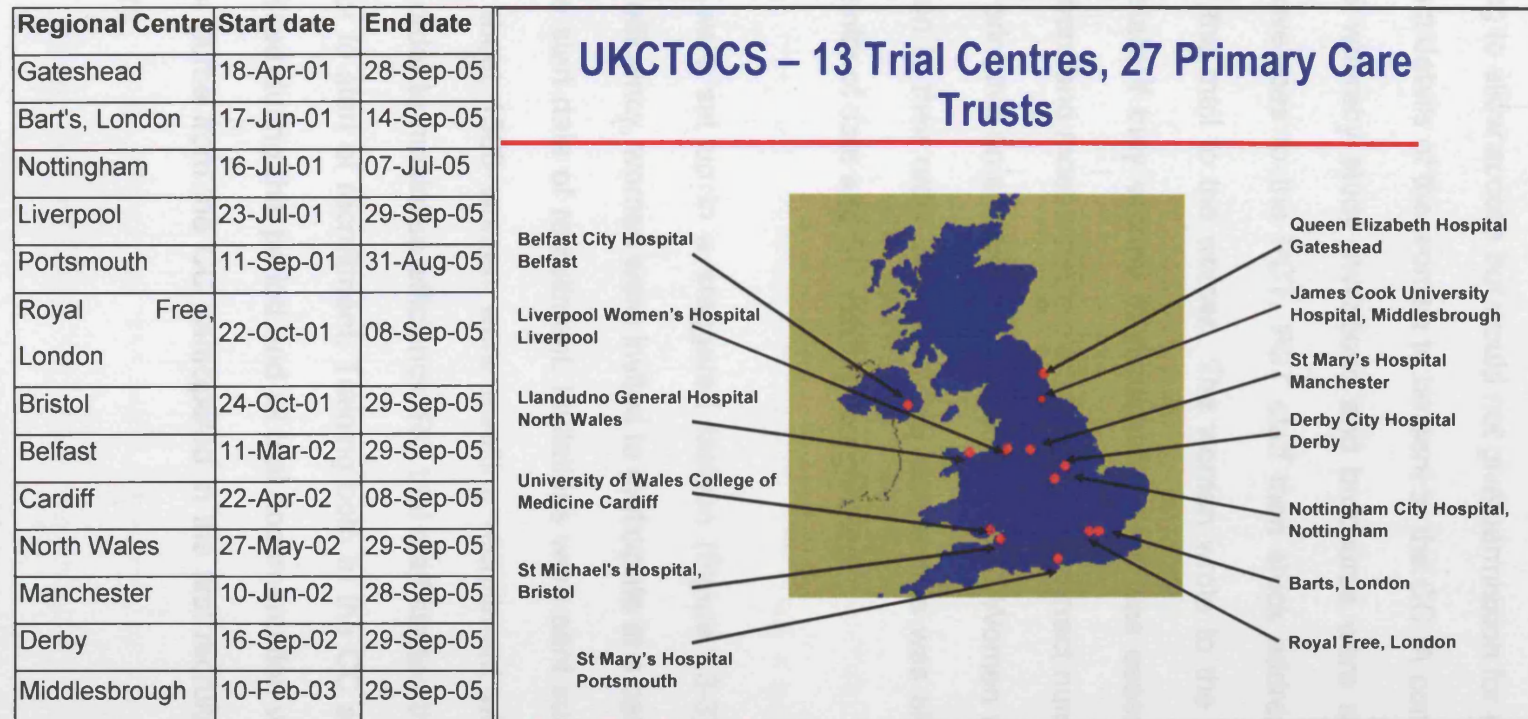


Figure 13-3: Location of UKCTOCS trial centres and start and end dates of recruitment

Caldicott Guardians for 5 PCTs refused access to contact details of women on their age/sex register. On exploring their concerns, it became clear they were willing to allow access but would not give permission for electronic files with contact details of the women to be sent to the CC. A compromise was negotiated whereby study invitations and brochures were sent in sealed franked envelopes to the PCT. PCT staff then stuck address labels and forwarded the mail to the women. The women wrote to the CC with their contact details if they wished to participate. As it was essential to obtain NHS numbers and most women did not know the correct number, the PCT agreed to print this on a corner of the address label. Women were asked to copy this on to their reply slip. The DMS programme was altered to allow manually entry of data and CC staffing reorganised.

The RCs were set up in a staggered fashion (Figure 13-3). In order to maximise efficiency, women were invited to participate at a centre 3 months prior to the start date of recruitment. Invitations were sent such that at the minimum about 1500 women were awaiting recruitment when a centre began. In order to maximise efficiency, RC trial staff started their posts two weeks prior to start of recruitment. Training both at the CC and at the RC was organised during this period and all trial documentation was delivered. The senior nurse from the CC participated in the first recruitment clinic at each centre.

There was national media coverage when the trial was launched. In addition as each RC came on line and women in the surrounding areas received

invitations to the trial, press releases, interviews on local radio and articles in local newspapers were organised. This was cost free. The impact of OC on women's lives, the benefits of the study, the major components of the study, the main inclusion criteria were emphasised. A website www.ukctocs.org was set up where both public and health personnel could obtain detailed information about the trial.

The target of 16,667 women in 3 years meant a weekly target of 120 women per week (based on 44 working weeks in a year). The RCs would need a minimum of 5 recruitment clinics a week, with 24 women recruited in each. In order to make this feasible and sustainable and to ensure that women were well informed about all aspects of the trial, it was decided to make a ten minute information video about the trial. It showed a group of women (CC staff and volunteers) attending for trial recruitment with one of the CC staff explaining the key aspects of the trial and taking questions. The video was made by an experienced BBC producer. Funding for making the video and for providing video players and TVs to each RC had to be found from sources outside the grant.

At recruitment clinics, appointment slots were set up such that 6 women attended together for a 45 minute appointment. After viewing the trial video, the research nurse led a group discussion. She then spent 5 minutes alone with each woman. A clerk assisted her by documenting attendance 'live' over the web browser and assisting the women in completing their recruitment data sheet. To facilitate recruitment, the data sheets for each

clinic were pre-printed at the CC with the volunteer's details and delivered two weeks ahead of the clinic along with barcoded labels.

There was close monitoring of acceptance rates and it was clear within the first 6 months that these were below the estimated 66%. Measures to improve acceptance rates were explored including simplifying the invitation letter and instituting local publicity. It was soon clear that instead of 300000, it would be necessary to invite about 1.2 million women. Early in the trial measures were instituted to ensure savings were made that would defray some of these costs. The MRC board was appraised well in advance and towards the end of recruitment awarded an extension and a supplementary grant.

Overall invitations were sent to 1,243,312 women, 1,079,515 directly by the CC and 163,797 by the PCTs covered by the RCs at Liverpool, Belfast and for a few months Gateshead. The acceptance rate varied between from 19% in East London (Barts) to 32% at Portsmouth. Overall 290,947 (26% of women excluding those who replied they were ineligible) replied they would like to participate in the RCT (Table 13-1). These women were sent detailed information about the trial and a recruitment appointment. 74743 withdrew or did not attend the appointment (Table 13-1).

There was weekly monitoring of recruitment figures. It became apparent that the number of women who failed to attend appointments varied between centres. To maintain recruitment, the number of women booked into a 45

minute appointment slot was increased at each centre to compensate for this so that an average of 100 women attended recruitment each week. The median time from recruitment to randomisation of a woman was 12.3 days (25th centile 8.5 days; 75th centile 15.5 days). The median number of women randomised per month was 4018 (mean 3861) (Figure 4). There were dips in numbers randomised in August and January each year following the holidays. The breakdown of randomisation by RCs is shown in Table 13-2 .

In 2001, the MRC published the Human Tissue and Biological Samples for use in Research - Operational and Ethical guidelines. In response to this, it was felt that more information should be provided to women about storage of excess serum samples for future studies and that the new MRC consent form should be adopted. Following ethical approval trial documentation was changed and the 50,000 women who had already been recruited were sent the additional information with the option to withdraw. None took up the option to withdraw. A ticker tape was added to the video which emphasised that excess serum would be stored for future ethically approved secondary studies.

UKCTOCS – RECRUITMENT AND RANDOMISATION

Table 13-1: Acceptances rates

Regional Centre	Invited	All acceptances including those known to be ineligible	Acceptance rate including known ineligible	Ineligible at invitation*	Acceptance rate excluding women known to be ineligible**
Gateshead	109054	33651	30.86%	8874	24.73%
Gateshead (PCT invited) ***	13000	1324			10.18%
Bart's	166988	39949	23.92%	10269	18.94%
Liverpool***	63987	14855			23.22%
Nottingham	77013	28924	37.56%	6999	33.62%
Manchester	133609	35109	26.28%	8938	20.99%
Derby	65445	24895	38.04%	5093	35.27%
Royal Free	133868	31171	23.28%	6415	21.03%
Portsmouth	95144	36490	38.35%	8738	32.12%
Bristol	74970	28613	38.17%	5703	33.07%
Belfast***	86810	16975			19.55%
Cardiff	96610	32710	33.86%	8753	27.27%
North Wales	73993	26666	36.04%	5134	31.27%
Middleborough	52823	16905	32.00%	3274	27.51%
Overall total	1243312	368237			25.34%
Total/ Average excluding Belfast and Liverpool	1079515	335083	31.04%	78190	25.66%

*This data is not complete as only an unknown proportion of ineligible women reply.

**Ineligible women not included in numerator or denominator

*** Due to the manner invitations are sent, only eligible women reply

Acceptance rate (%)	Code
≤20	
>20-25	
>25-30	
>30-35	

UKCTOCS –RECRUITMENT AND RANDOMISATION

Table 13-2: Recruitment and randomisation per year at each UKCTOCS regional centre

Regional Centre	No of PCTs	No of GP practices	Number of women randomised						% of target	No of years of active recruitment
			2001	2002	2003	2004	2005	Total		
Gateshead	3	252	2243	6119	4551	1850	2558	17321	103.92%	3.9
Bart's	3	454	1639	6808	4671	4575	2081	19774	118.64%	4.2
Liverpool	3	191	1107	4102	2060	23*	2800	10092	60.55%	2.5
Nottingham	1	195	1641	5084	4877	3721	1455	16778	100.67%	3.9
Manchester	5	385	1	2666	5792	4995	3068	16522	99.13%	4.0
Derby	1	139	3	1513	5015	4472	3928	14929	89.57%	3.9
Royal Free	3	502	474	3777	4370	3981	4289	16891	101.34%	3.9
Portsmouth	2	291	945	4662	5392	4942	3246	19187	115.12%	3.5
Bristol	1	178	428	4132	4171	3777	4020	16528	99.17%	3.4
Belfast	2	148		3309	3302	3837	3137	13585	81.51%	3.3
Cardiff	1	198	2	2879	4831	4671	4368	16751	100.50%	3.2
North Wales	1	167		1919	4340	4201	3892	14352	86.11%	3.0
Middlesbrough	1	86	3	3	4138	3785	1999	9928	None set	2.6
Total	27	3186	8486	46973	57510	48830	40839	202638	101.32%	45.4

*Recruitment was suspended due to staffing issues

UKCTOCS –RECRUITMENT AND RANDOMISATION

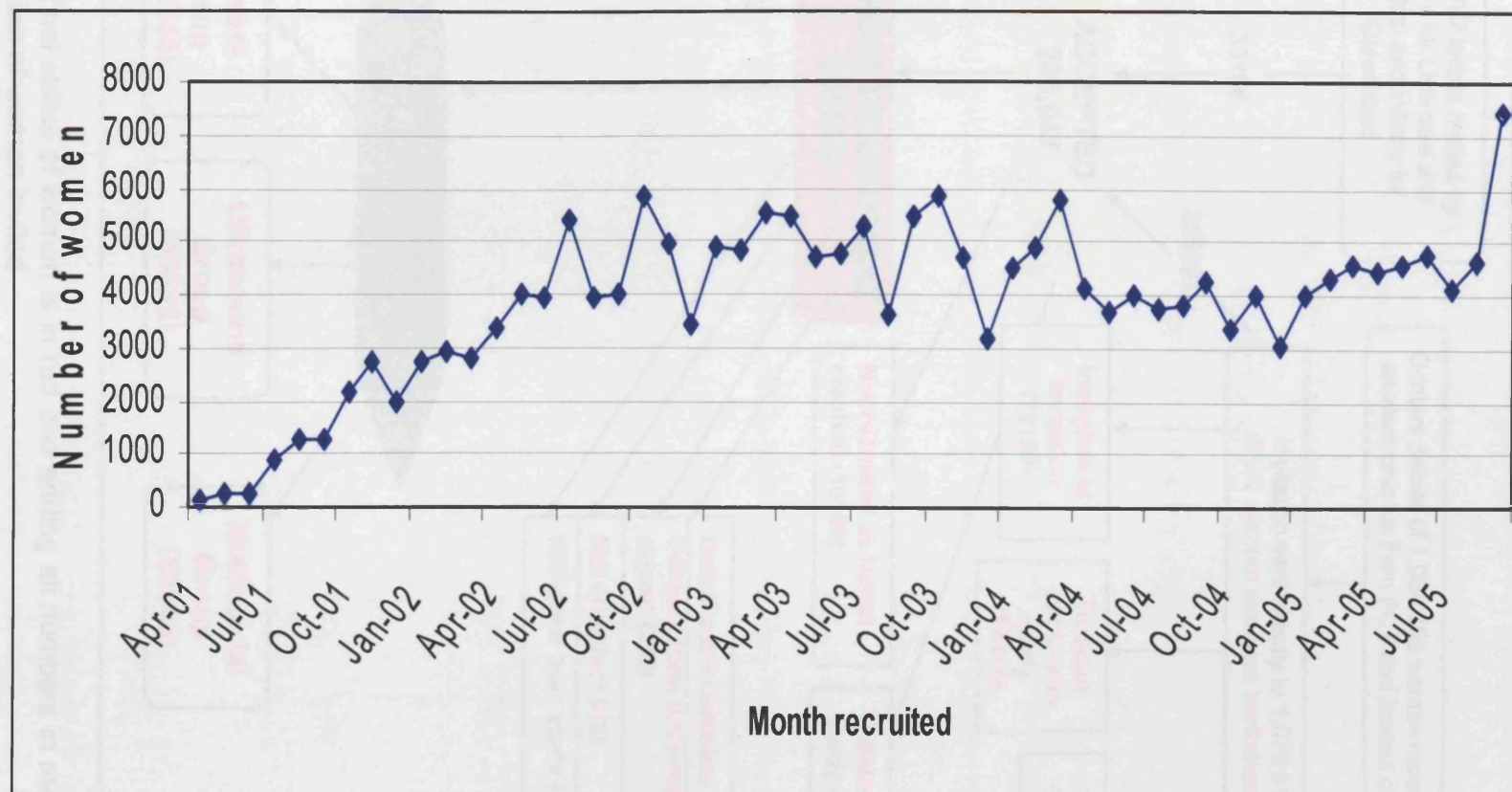
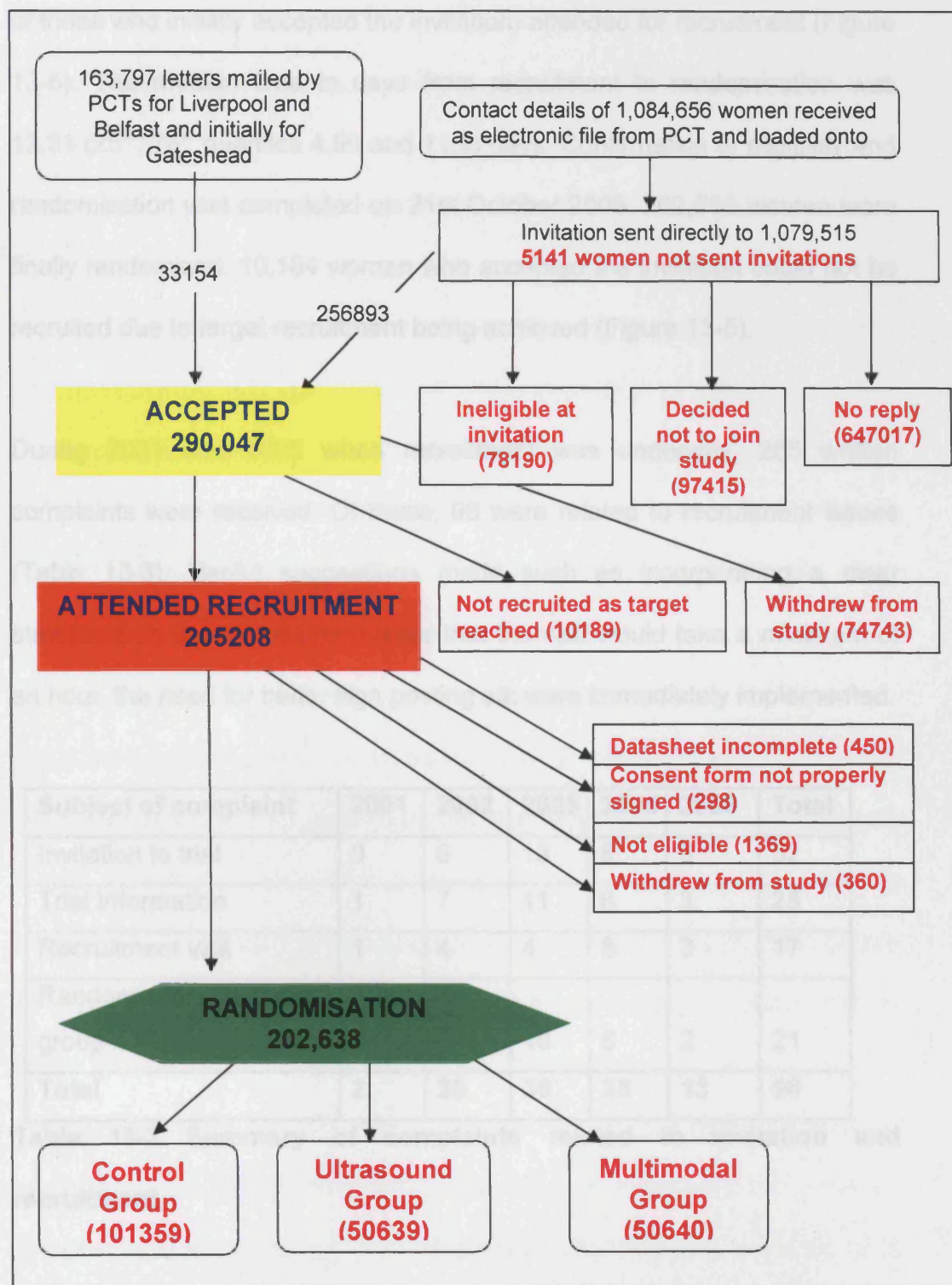


Figure 13-4: Number of women randomised per month into UKCTOCS

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UKCTOCS –RECRUITMENT AND RANDOMISATION



Note that final status of women is in red and adding all numbers in red will equal number of women invited

Figure 13-5: Status of all women at the end of recruitment

Between 17th April 2001 and 29th September 2005, 205208 women (71% of those who initially accepted the invitation) attended for recruitment (Figure 13-5). The median time in days from recruitment to randomisation was 12.31 (25th, 75th quartiles 4.56 and 11.9) days. Confirmation of eligibility and randomisation was completed on 21st October 2005. 202,638 women were finally randomised. 10,184 women who accepted the invitation could not be recruited due to target recruitment being achieved (Figure 13-5).

During 2001 and 2005 when recruitment was underway, 265 written complaints were received. Of these, 98 were related to recruitment issues (Table 13-3). Useful suggestions made such as incorporating a clear statement on the appointment letter that the visit would take a minimum of an hour, the need for better sign posting etc were immediately implemented.

Subject of complaint	2001	2002	2003	2004	2005	Total
Invitation to trial	0	6	13	8	5	32
Trial Information	1	7	11	6	3	28
Recruitment visit	1	4	4	5	3	17
Randomisation to control group	0	3	10	6	2	21
Total	2	20	38	25	13	98

Table 13-3 Summary of complaints related to invitation and recruitment

192624 serum samples were obtained at recruitment and stored for use in future studies.

13.4 Discussion

A total of 205,208 women attended for recruitment at 13 centres in the UK between April 2001 and September 2005. 202,638 were randomised, making UKCTOCS the largest ever RCT undertaken. Next in size are the UK Single Flexible Sigmoidoscopy screening trial (FLEXISIG) with 170,432 men and women¹⁶⁹ and the Women's Health Initiative prevention trial with 161,808 postmenopausal women¹⁷⁰. The only trial to report on larger numbers of participants is the UK Trial of Early Detection of Breast Cancer (TEDBC) set up in 1979 which involved 236,103 women. However TEDBC was a non-randomised study with 108,980 women recruited to the study arm and a comparison group of 127,487.¹⁷¹

UKCTOCS is the largest OC screening trial. Given the size and the RCT design, it should answer definitively whether screening will have a mortality impact. The largest OCS trial reported so far involved 51,500 Japanese women who underwent a transvaginal scan during annual cervical cancer screening. The authors noted that the percentage of Stage I ovarian cancer cases treated in the department increased after introduction of screening from 29.7% to 58.8%¹⁰ The lack of a control group, the wide age range of participants, the low numbers of OC detected and the lack of data on screen negative cancers made it impossible to draw any definitive conclusions. In an earlier RCT of OCS involving 22,000 volunteers, women with OC in the screened arm were noted to have a survival benefit⁸. The size and design of UKCTOCS should also make it possible to address comprehensively

performance characteristics of the screening strategies, physical and psychological morbidity, cost, acceptability and compliance.

The OCS component of the general population Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the US will probably be larger than the Japanese cohort. The number of women eligible for the ovarian arm of this trial is not yet clear. Between autumn 1993 and June 2001 (8.3 years) 78,237 women aged 55-74 were recruited via 10 centres. A proportion are not eligible for the OC screening arm as they had previously undergone bilateral oophorectomy¹⁷². The OC prevalence screen in the trial involved 28,816 women¹³³. There has been discussion with the PLCO investigators and in principle a meta-analysis of the two trials has been agreed. No other trials are underway in the general population. In the high-risk population however, several smaller single arm trials are underway. These will not address the core issue of impact of OCS on disease mortality.¹⁷³

The plan was to set up 12 regional trial centres (RC) in the UK in a staggered fashion over the course of 12 months. It has been suggested based on anecdotal data that staggering recruitment may help to prevent fall in recruitment with time.¹⁶⁸ 11 centres commenced recruitment within 14 months of start of recruitment with the 12th starting recruitment at 17 months. The key reason for the 5 month delay was that 4 of the pre-identified 12 RCs dropped out. As a result, negotiations and approvals had to recommence to set up four new RCs. A recent review of UK multicentre trials reported that in

20% of trials, a proportion of pre-identified centres did not participate and 45% of trials had to recruit new centres.¹⁶⁷ It is important in the planning of multicentre trials, that the list of pre-identified centres outnumbers that finally required especially if centres have to make significant long term infrastructure commitments. The review found no common reason for the fall out. In UKCTOCS, the main issue were inability of hospital management to commit to space requirements for the 10-year lifespan of the trial and retirement of key clinicians. Space to run clinical trials is increasingly difficult to find in the current NHS and will be even more so as Trusts use Private Funding Initiatives to modernise their hospitals. It is vital that trialists and funding agencies such as the MRC and Cancer Research UK (CR UK) highlight this issue. Support from the Department of Health and the UK Clinical Research Network for dedicated clinical research facilities in teaching and large district hospitals is essential if multicentre clinical trials are to continue. In this context, the Wellcome Trust Clinical Research Facility in Manchester (one of five such facilities in the UK) which hosts the UKCTOCS Manchester provides a valuable model of a joint NHS/academic environment, staffed and equipped to promote high quality studies (www.crf.man.ac.uk).

The negotiations and effort involved in setting up an additional 13th centre paid dividends when one of the initial 12 centres was forced to suspend recruitment for over a year due to staffing issues (Table 2). Grant funding for clinical trials in the UK leave little leeway for such problems which though unpredictable, have been reported frequently.¹⁶⁸ Investigators should

prepare and budget contingency plans in case of poor recruitment at the start of trials which funding agencies and sponsors should be willing to release with if recruitment falters.

Trial centres need to be chosen such that they are able to recruit a representative group of women. Equally important they need to have the skills required for delivery of the intervention and/or treatment. Centres for UKCTOCS were chosen so that gynaecological oncology expertise in managing ovarian cancer was coupled with geographical location of centres so that they covered a representative sample of the UK female population. Centres were planned for England, Scotland, Wales, and Northern Ireland but pre-identified Scottish centres dropped out mainly due to logistical issues. Participation was not restricted to academic centres. This is supported by the work of Prescott RJ et al on cancer trials networks.¹⁶⁸

Women aged 50-74 were randomly chosen women from the age/sex registers of participating PCTs and sent personal invitations. The alternative option would have been to advertise the trial extensively and let women self refer. This is the strategy adopted by most OCS screening trials such as PLCO trial¹⁵⁸, Bart's OCS trials^{8 51 57}, University of Kentucky Screening Trial⁹. Women who volunteer to participate in research are often more educated and informed¹⁷⁴⁻¹⁷⁶. It was felt that trial participants may be more representative of the general population if all potentially eligible women in the target area were invited. Logistically this approach had numerous advantages: better control of recruitment rates and logistics by varying the

rate of invitation; decreased data entry as electronic files from the PCT were directly uploaded into the DMS; vastly improved accuracy with regard to each woman's NHS number and to a lesser extent contact details of her GP. Our experience from previous trials^{8 57 166} is that most women do not know their NHS number. It is however essential in the UK for flagging women via the Office of National Statistics for follow up. The cost of the flagging study is directly correlated to availability of the NHS number of the individual. Finally this mode of invitation allows data to be gathered on the number of women invited, the variation in acceptance rate between regions and the age and deprivation status (based on postcode) of women who do not participate.

There was national media coverage when the trial was launched and local press releases when each RC started recruitment. This was cost free. Mass broadcast (television and radio) and print media (regional, city, and neighbourhood newspapers and flyers) are 'low effort, high yield' recruitment strategies¹⁷⁷ used by most trialists¹⁷⁸. However, in UKCTOCS a balance had to be struck between too much and too little publicity as women could not self refer and could only enrol if they received an invitation. Hence no posters and flyers were put up in GP surgeries, well women clinics etc. It is possible that such additional measures might have increased acceptance rates.

In UKCTOCS, permission was requested from Caldicott Guardians (data controllers for PCTs) for an electronic file with contact details of women

aged 50-74 on the age /sex register so that the CC could send a personalised invitation. There was disagreement among the data controllers on interpretation of the Data Protection Act 1998 (www.informationcommissioner.gov.uk). There is a research exemption in this act which allows processing of personal data if it is necessary for medical research and undertaken by a health professional. The majority (22) of Caldicott Guardians felt that the trial request fulfilled this criterion. However, Caldicott Guardians for 5 PCTs refused permission. The requests relate to 2000/2001. Since then there has been increasing guidance provided by the Department of Health (DoH) on the conduct of clinical trials. It is essential that clear guidance about the 1998 Act as it relates to research is circulated to data controllers by the DoH and there is a forum for appeals and discussions. 32 women of the 1.2 million invited complained about being sent an invitation. The low complaint rate suggests that British women are supportive of use of their personal data for invitation to trials.

Barbara Farrell lists lateral thinking and a practical business like approach to getting the job as essential to managing trials successful.¹⁷⁹ For the 5 PCTs, an alternative plan was drawn up and the DMS modified. Trial invitations were sent in sealed franked envelopes to these PCTs whose staff then stuck address labels and posted them. Women replied to the CC with their contact details if they wished to participate. Acceptance rates at these PCTs (Liverpool and Belfast) were similar to those for PCTs serving Manchester and Gateshead (Table 1). This suggests that the lack of a personalised invitation does not impact on acceptance rate. The main disadvantage was

that mailing the invitations was dependent on the work priorities of the PCT staff and often there were significant delays which led to underutilised recruitment clinics. In addition the handwritten acceptance sheets with personal details required data entry and all of this resulted in additional consumable and staff costs. In these centres, it is not possible to estimate the number of ineligible women in the invited population.

In UKCTOCS, individual GP practices were not sent patient lists so that women already diagnosed with ovarian cancer or suffering from terminal illnesses could be excluded from invitation. One of the reasons cited for requesting GPs to 'clean up' lists is concern that trial invitations may cause distress to women already diagnosed with ovarian cancer. However, the prior experience of the researchers and advice from patient groups such as OVACOME was that the majority of women with ovarian cancer were supportive of the research efforts. This was borne out in that only 4 women from over 1.2 million invited reported distress on receiving an invite following a diagnosis of ovarian cancer. Based on an incidence of 48.9/100000 in this population, about 587 women with ovarian cancer must have been contacted.

An issue that is often debated is whether acceptance rates could be increased by GPs excluding ineligible individuals after checking the lists. In the FLEXISIG trial local health authorities identified 375,744 men and women aged between 55 and 64 years. General practitioners on checking the lists identified 7602 (2%) as being ineligible for the trial with the number

excluded per practice varying from 0 to 144 (median 11). 85 of the 505 practices taking part in the study did not exclude any of their patients. In UKCTOCS, such an approach would have involved contacting and getting agreement from each of 3186 GP practices located in the 27 participating PCTs, regular delivery of lists to the practices as invitations spanned 3 years, checking of the lists by practice staff in a timely manner to maintain the recruitment rate. The virtual lack of complaints in UKCTOCS by women or GPs after mailing of over a million women across England, Wales and Northern Ireland and the small number of people excluded in FLEXISIG after contacting 505 GP practices, seems to suggest that in UK inviting women from PCT lists for trials without explicit permission from their GPs is acceptable and efficient. The massive effort required in 'cleaning up lists' does not seem justified.

Inviting women from the age sex registers had not been piloted during the UKCTOCS pilot. However, two earlier randomised control trials of OCS using ultrasound had reported on acceptance rates. Parkes et al in 1994 reported that 82% of 8678 women, aged between 50 and 64 attending for NHS breast cancer screening between September 1989 and February 1993 at Reading England accepted the invitation to participate in an RCT of OCS using transvaginal ultrasound ¹²¹ Higher acceptance rates can be anticipated for screening trials if invitations are restricted to women regularly attending the breast or cervical screening as these populations are self selected with regard to their beliefs in screening. However both these national screening programmes are limited to women aged below 65 and

therefore inviting women participating in these national programmes was not considered an appropriate option for UKCTOCS where the aim was to screen women aged 50 to 74.

Tabor et al published an acceptance rate of 64.3% (950 of 1477 eligible women) in a population based study of women aged 46 to 65 years living in Copenhagen, Denmark¹⁵² and in planning for UKCTOCS, this figure was adopted. It proved to be an significant overestimate of acceptance rates. A four-fold increase in number of women invited was required to ensure that target recruitment was met. Of 1,243, 312 women invited to participate in a RCT of OCS, 26% (excluding those known to be ineligible) answered that they would like to take part, with the highest rates of acceptance (30-32%) in Bristol, Portsmouth, Nottingham and North Wales and the lowest rates (19%) in inner city London. This was similar to the uptake rate of 24% for colorectal cancer screening at Dundee¹⁸⁰. However, in the FLEXISIG trial, overall acceptance rates were 55%. It needs to be clarified that this was in response to the question whether they would take up the offer for a bowel cancer screening test if invited rather than whether they would participate in an RCT of screening. About 4% of invites were returned undelivered in FLEXISIG. It was not possible to estimate these numbers in UKCTOCS as the envelope did not have the trial address printed on the outside, a simple but easily overlooked point. Previous studies have shown that uptake of screening is related to socioeconomic deprivation. It is possible to derive a deprivation index such as Townsend Index based on 2001 Census data using a woman's postcode. An analysis of any association between

deprivation, age and distance from the regional centre on acceptance rates is underway.

Automated central allocation of regional centre recruitment appointments by the customised data management system and close monitoring of under filled recruitment clinics ensured that the median number of women recruited monthly was over 4000 women once all 12 centres were active (Figure 13-4). Meeting recruitment goals for any trial is often more challenging than anticipated. This is especially so for longitudinal RCTs that span many years. Time for the recruitment phase often needs to be extended beyond original plans by an average of 27%. In UKCTOCS, it was originally planned that each of 12 RCs would have 3 years to recruit the target population i.e.. 200,000 women would be recruited in 36 centre years. It took 45.4 centre years to recruit 202,638 women (Table 13-2). This equals a 26% extension of the recruitment phase when compared to the original estimate.

In terms of time, recruitment in UKCTOCS took 4.3 years (May 2001 to September 2005), which translates to an average of 47,125 women randomised per year. Randomisation rates were exceeded only in the FLEXISIG trial with an annual randomisation rate of 68,173 per year¹⁶⁹. However in this trial participants were not recruited in the usual manner. Individuals who answered 'Yes' to the question – 'If you were invited to a bowel cancer screening test, would you take up the offer?' were randomised. Individuals were not required to sign consent to participate in a RCT or for flagging through ONS¹⁸¹. Only 40,674 of the 170,483 individuals

who underwent screening signed consent¹⁶⁹. If such a design were to be adapted for use today, a detailed information leaflet about the trial and clear specific consent to participate in an RCT would be required before randomisation and flagging via the Office of National Statistics. However, the design of postal recruitment of women to the screening trial with attendance in person of only those in the study arm is attractive logistically and worth exploring further. The highest recruitment rate for a US trial was achieved by the WHI trial with average annual recruitment of 32,362 women. On the whole, recruitment to large UK RCTs seems to be more efficient in terms of time and resources than US trials.

With recruitment complete in UKCTOCS, the trial is set to answer key questions on impact of screening on ovarian cancer mortality, physical and psychological morbidity, compliance, and cost. The focus in the coming years is on ensuring compliance with screening. The serum bank and follow up via ONS will allow discovery and validation of novel serum markers for ovarian cancer and other diseases.

14 BASELINE CHARACTERISTICS

14.1 Introduction

This paper describes the characteristics of the women recruited to the UKCTOCS trial.

14.2 Methods

At recruitment, the women were asked to complete an 18 item questionnaire which is 2 pages long (A4 size). It includes information regarding age, height, weight, country of birth, ethnic origin, age at menarche, reproductive history including treatment for infertility and sterilization, date of last menstrual period, previous oophorectomy, previous oral contraceptive use, HRT use, previous hysterectomy, participation in another ovarian cancer screening trial, personal history of cancer and family history of breast and ovarian cancer. At the coordinating centre, the recruitment questionnaire was scanned electronically using computerised intelligent character and optical mark reading software (TeleForm) allowing rapid and accurate data entry. Any inconsistency or information that was not recognised by the data capture software was verified manually by trained data entry staff, who also validated computer-interpreted data and checked each questionnaire to confirm whether signed consent for follow up has been granted. If there was any missing data in the fields on the data sheet that were mandatory to confirm eligibility, then the DMS assigned the women to status 'incomplete'

and a letter was sent requesting data. If there was no response, the woman was contacted by phone call. No woman with incomplete data was randomised.

All entries of weight over 180kg and less than 30kg, height over 210cm and less than 75cm and pregnancies >12 were checked against the recruitment questionnaire and any data entry errors were corrected.

Analysis involved summative statistics using frequency distributions and median (quartiles). Trends and differences in baseline characteristics such as OCP use, hysterectomy, tubal ligation, no of pregnancies, BMI were explored between women stratified according to year of birth (1925-30; 1930-35, 1935-40, 1940-45, 1945-50, 1950-55) and age at randomisation (50-54, 55-59, 60-64 and 65 or over). The change in current HRT use over time was also assessed by considering the proportion (%) of women randomised each month who were using HRT when they attended for recruitment. 95% confidence intervals for the proportion estimate were used to validate any apparent trends. The extent of missing data was known to be very limited and so such records were discarded in the analysis without concern of bias.

14.3 Results

The statistics presented here are based on data collected at recruitment of the entire cohort of 202,638 postmenopausal women. They were recruited

UKCTOCS - BASELINE CHARACTERISTICS

between April 2001 and September 2005. Majority of the women belonged to cohorts born in 1940-45 and 1945-50 (Table 13-4). Groups <1000 in number are highlighted and these groups have been omitted from all birth cohort analysis

Table 14-1: Women grouped according to birth cohort and year of randomisation

Year of birth	Year randomised					Total
	2001	2002	2003	2004	2005	
1925-30	435	1325	755	80*		2515
1930-35	1256	6044	6682	8927	3283	26192
1935-40	1831	9457	10427	10401	9336	41452
1940-45	2231	11982	14280	10431	12103	51027
1945-50	2329	14308	17740	11898	9290	55565
1950-55	404	3857	7626	7093	6827	25807
Total	8486	46973	57510	48830	40839	202638

Groups <1000 in number are highlighted and these groups have been omitted from all birth cohort analysis

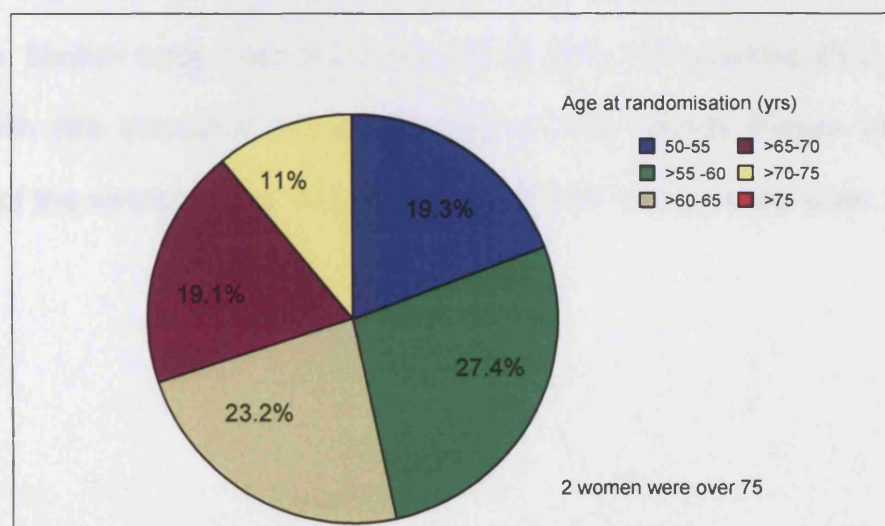


Figure 14-1: Age of women on date of randomisation into UKCTOCS

96.4% of the women were White with Black Caribbean (1823) and Indian (1180) forming the next largest ethnic groups (Table 14-2). 73.6% of the non-white population were recruited from the London centres. 84% of the women were born in England and Wales (Figure 14-3).

Table 14-2: Ethnicity

Ethnicity	Number	Percent
White	195274	96.4
Black Caribbean	1823	0.9
Indian	1180	0.6
Black African	761	0.4
Chinese	376	0.2
Pakistani	190	0.1
Black other	185	0.1
Bangladeshi	111	0.1
Other	1695	0.8
Not stated	1043	0.5
Total	202638	100

Median height of the trial participants was 162.6cms and median weight was 67.6kgs. Median body mass index was 25.78 (25th, 75th quartiles 23.3 and 29.1) with little change in women grouped by birth cohorts (Figure 14-2). 57.7% of the women had a BMI of ≥ 25 with 20.6% being obese (over 30).

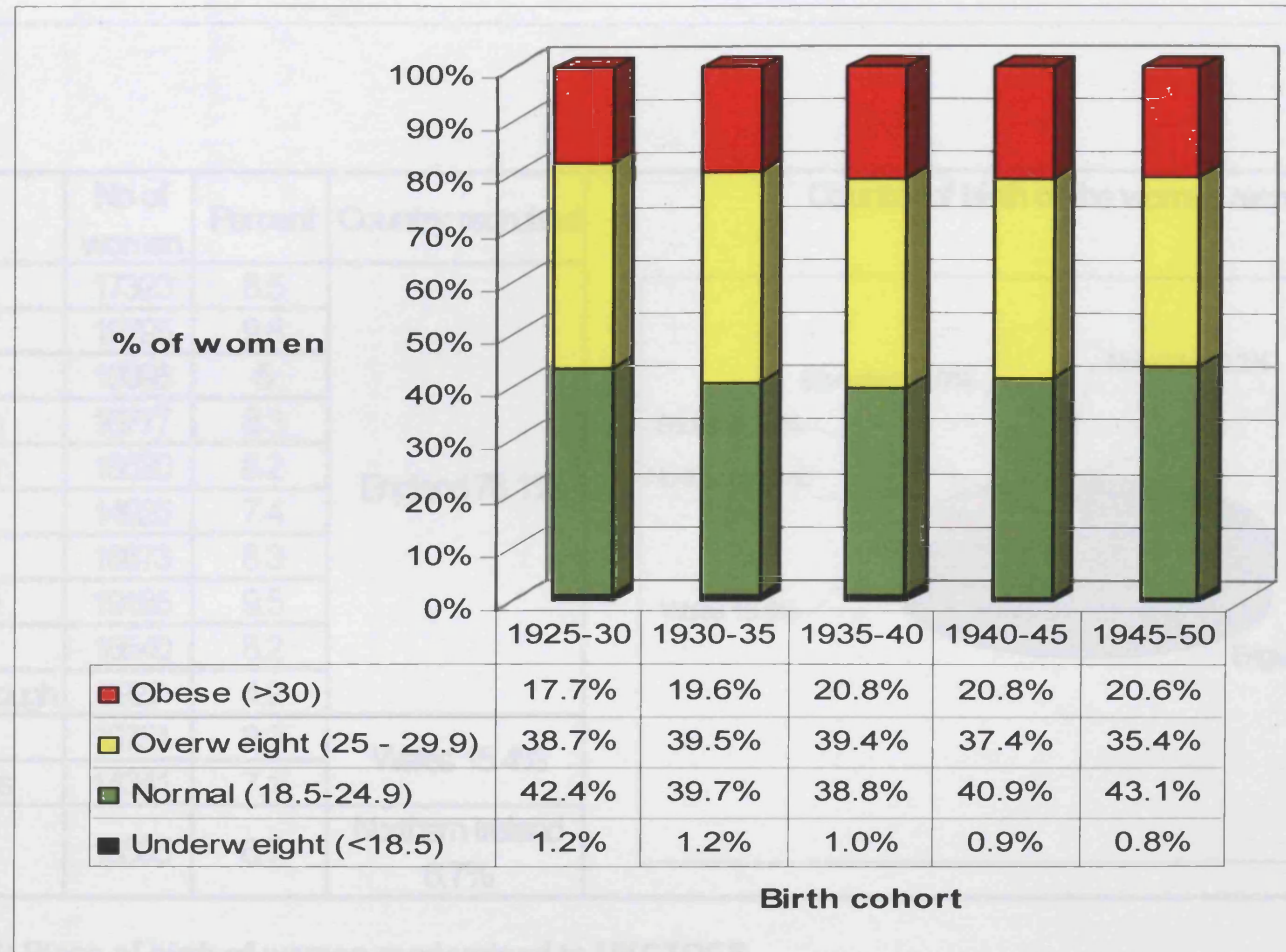


Figure 14-2: BMI at recruitment in women grouped by age

UKCTOCS - BASELINE CHARACTERISTICS

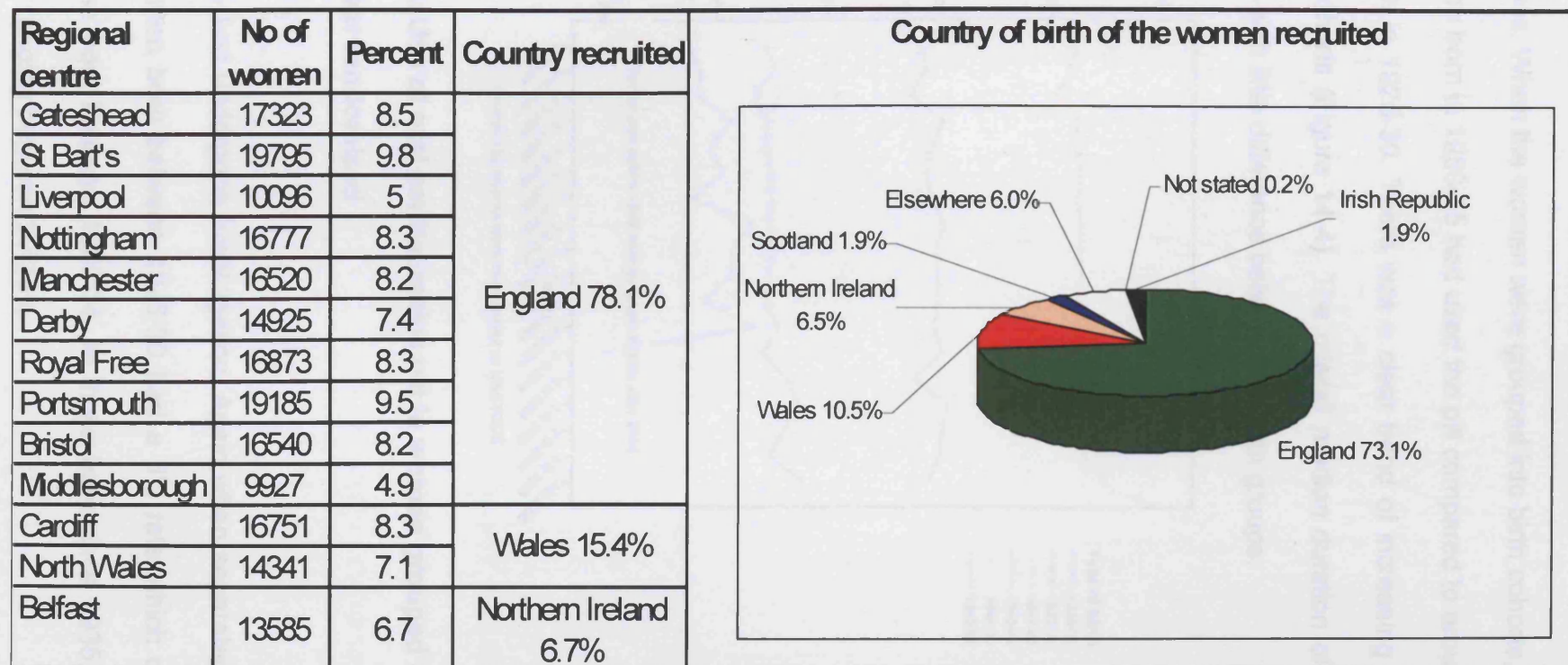


Figure 14-3: Place of birth of women randomised to UKCTOCS

Median age at menarche was 13. 59.6% of the women had used oral contraceptives. When the women were grouped into birth cohorts, over 80% of the women born in 1950-55 had used the pill compared to around 22% of women born in 1925-30. There was a clear trend of increasing pill use in later birth cohorts (Figure 14-4). The overall median duration of OCP use was 5 years with little difference between the birth groups.

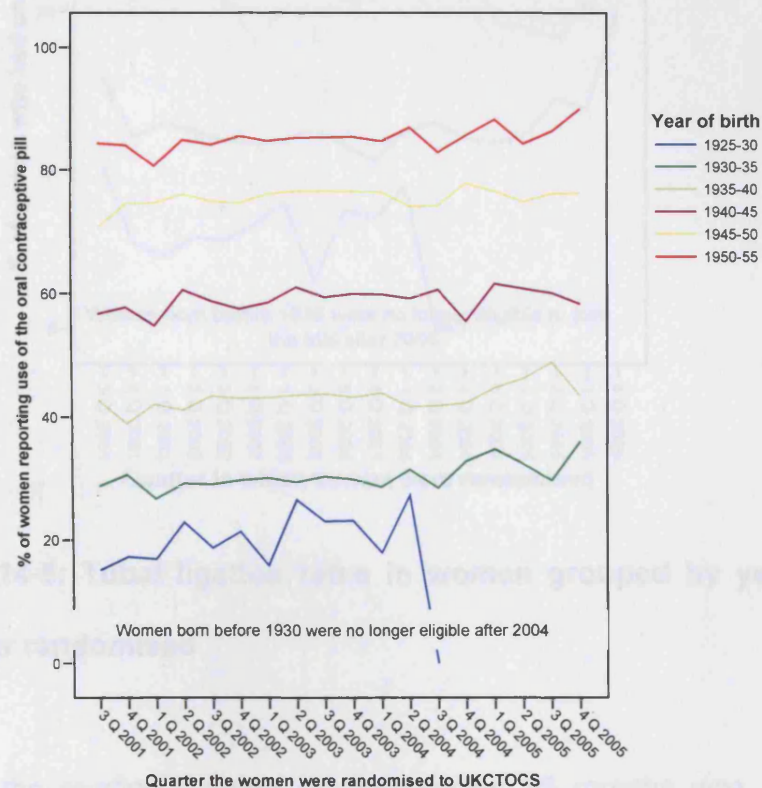


Figure 14-4: Use of oral contraceptive pill in women grouped by year of birth and year randomised

Overall 21% had undergone tubal ligation. Again when separated into birth cohorts, women born between 1925-30 had a 6% rate which doubled to 12% in those born between 1930-35. In those born since 1935, the rates were similar ranging between 20-25%.

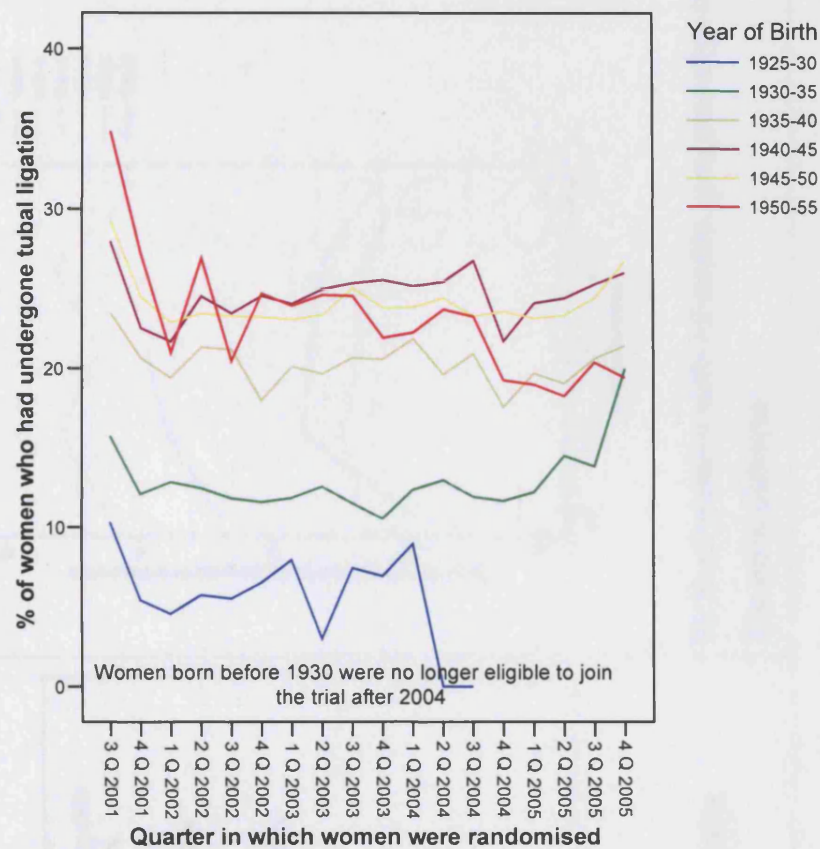
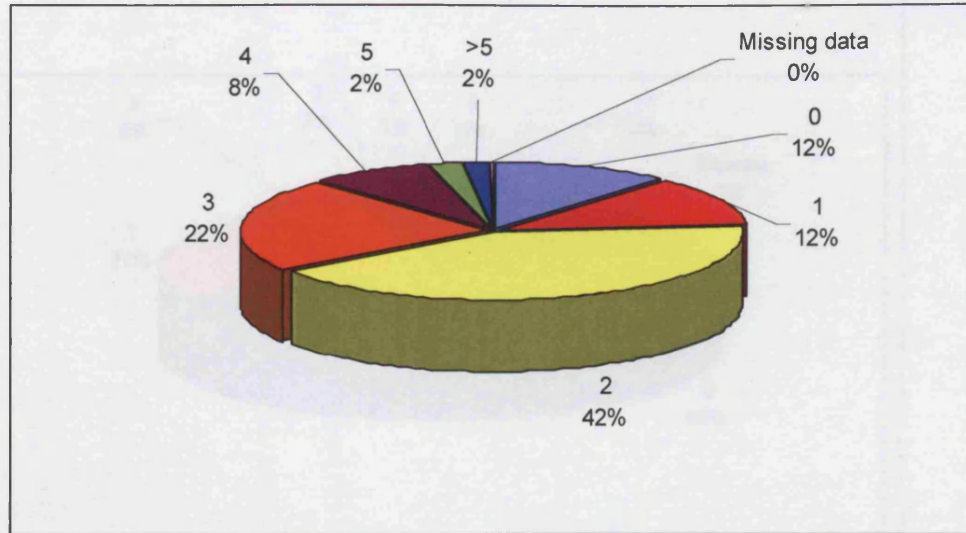


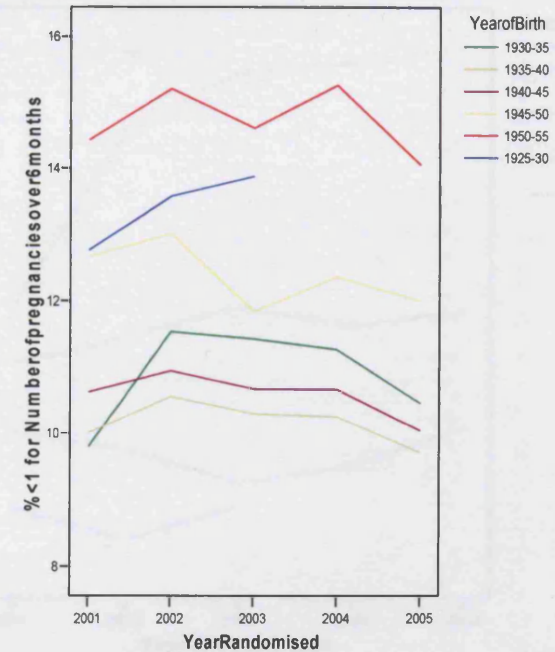
Figure 14-5: Tubal ligation rates in women grouped by year of birth and year randomised

Overall the median number of pregnancies >6 months was 2. 69% of women had not had a pregnancy <6 months. There were clear differences between the birth cohorts in terms of number of viable pregnancies (Figure 14-6 and Figure 14-7).

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A. Overall distribution of number of pregnancies > 6 months

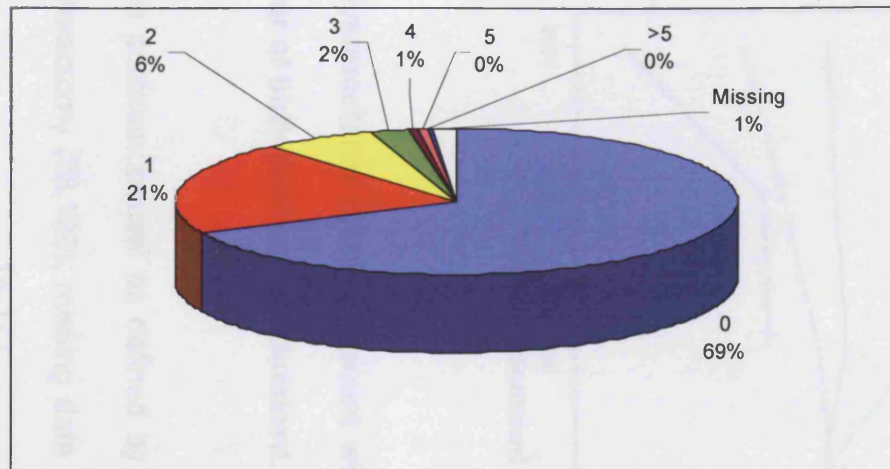


B. % of women with >2 viable pregnancies in the birth cohorts

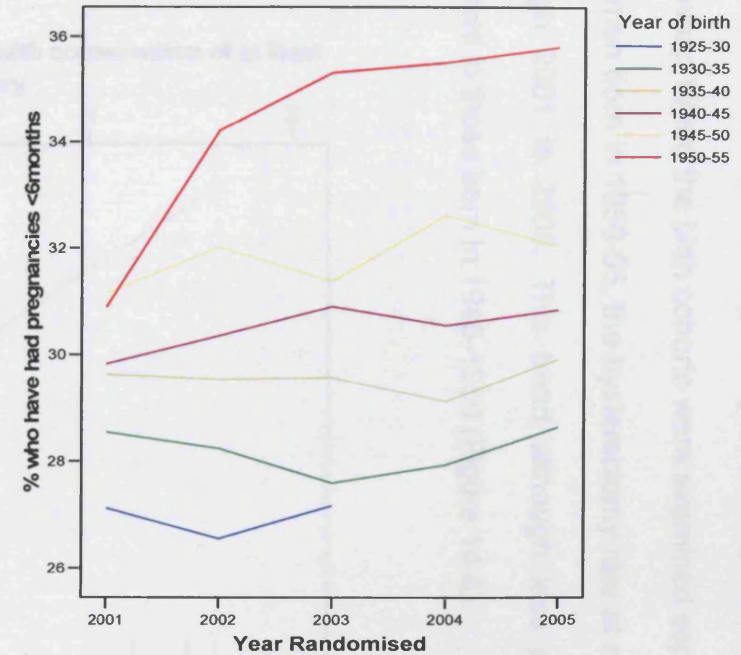
* There were only 2595 women in the 1925-30 cohort.

Figure 14-6: Distribution of viable (>6 months) pregnancies

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A. Overall distribution of number of pregnancies < 6 months



B. % of women with 1 or more pregnancy less than 6 months in the birth cohorts

Figure 14-7: Pregnancies below 6 months

18.9% of women had undergone hysterectomy with conservation of at least one ovary. When the birth cohorts were examined separately and over time, in women born in 1950-55, the hysterectomy rate at recruitment fell steadily through 2001 to 2005. This trend although less pronounced was also apparent in those born in 1945-1950 (Figure 14-8).

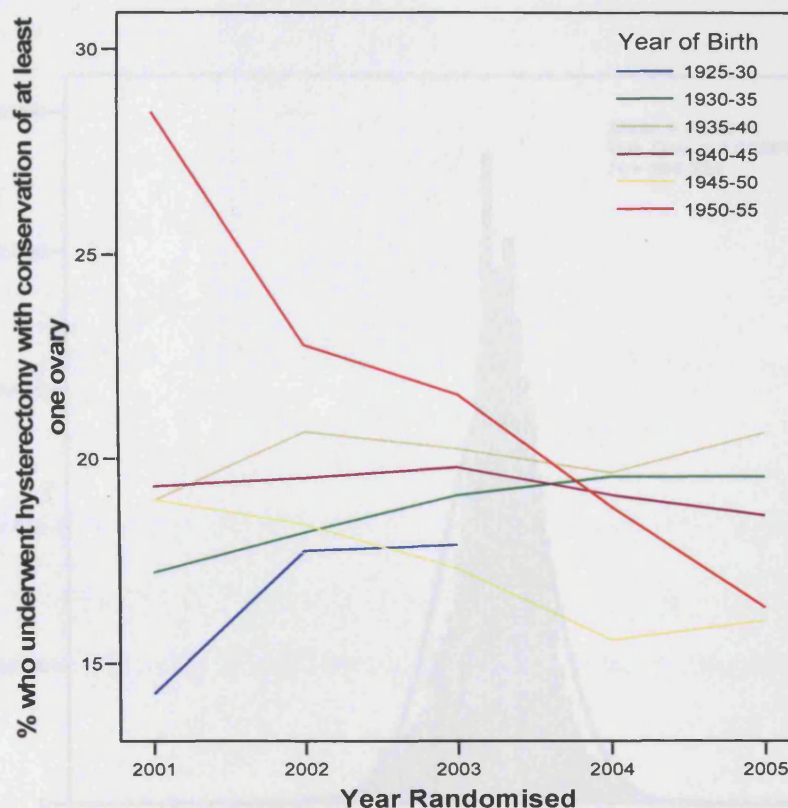


Figure 14-8: Hysterectomy rates in women with ovarian conservation grouped by year of birth and year randomised.

All women were postmenopausal as defined by eligibility criteria. Women who had a hysterectomy (38,120); missing data (4) and those with age of

menopause < stated age of menarche (100) were excluded. In the remaining 164,324 women, the median age at menopause was 50.66 years (mean 50.35; SD 4.32; 25th, 75th quartiles 48.15 and 53.15). If the women on HRT at recruitment (27,577 were excluded), the median age at menopause in the remaining 137,059 women was 50.5 years (mean 50.2; SD 4.83; 25th, 75th quartiles 48 and 52.95) (Figure 14-9).

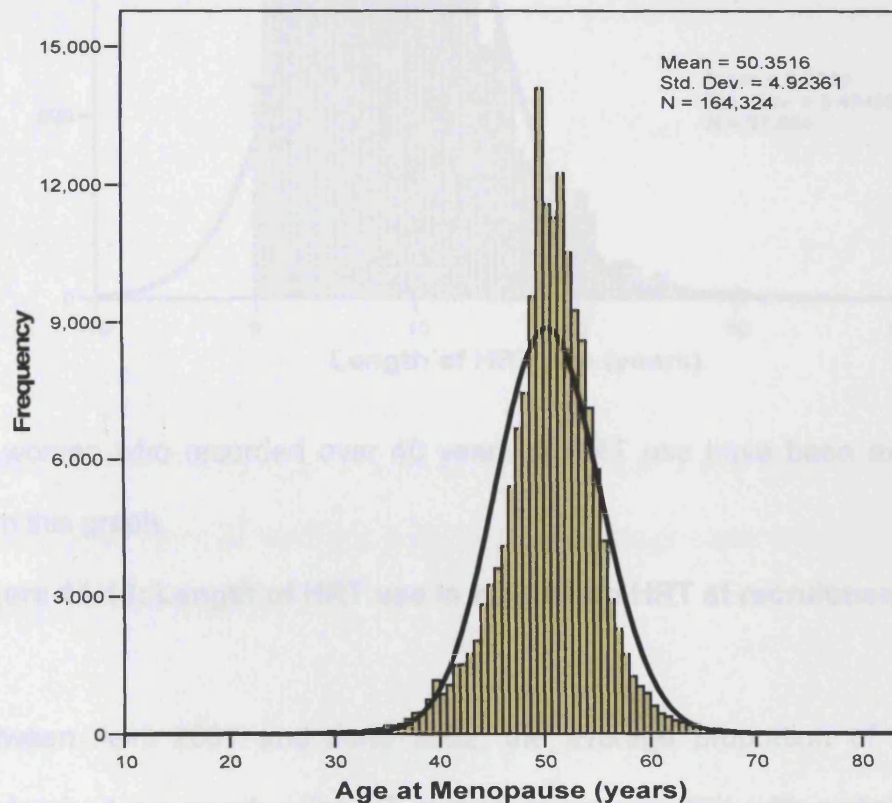
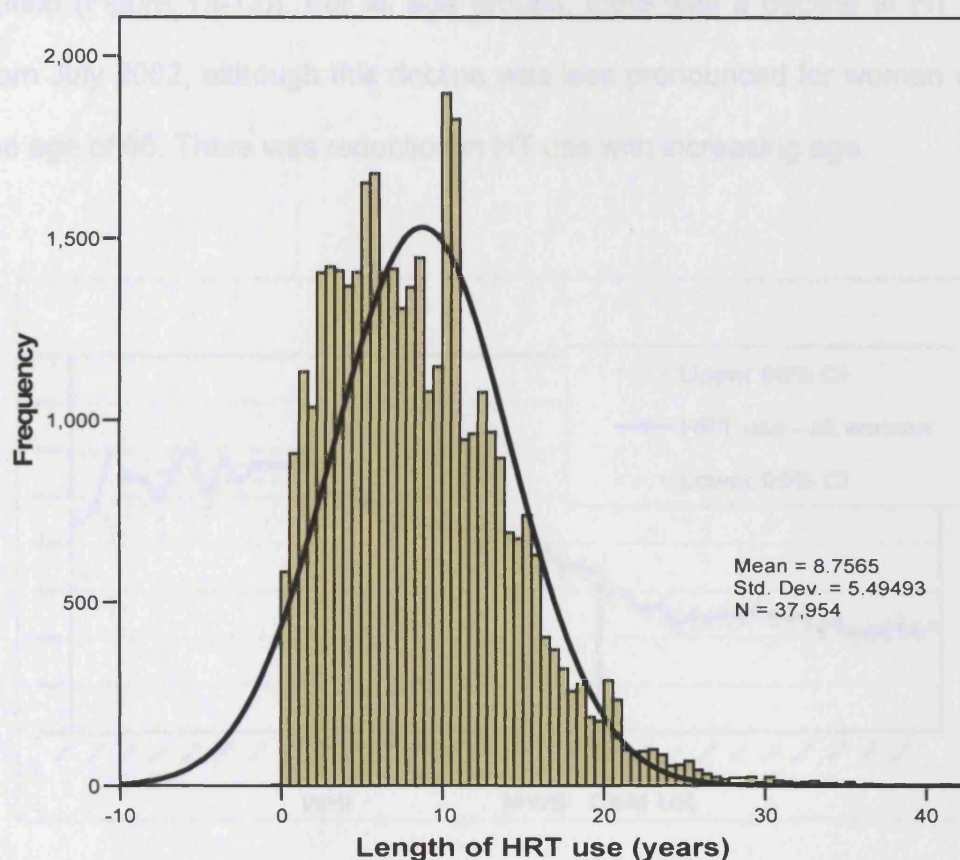


Figure 14-9: Age at menopause in women with an intact uterus

Overall 18.75% (38002) of women were using hormone replacement therapy (HRT) at recruitment. The median duration of HRT use was 8.15 years (mean 8.8; SD 5.72; 25th, 75th quartiles 4.5 and 12) years.



48 women who recorded over 40 years of HRT use have been excluded from this graph.

Figure 14-10: Length of HRT use in women on HRT at recruitment

Between April 2001 and June 2002, the average proportion of women randomised per month using HT at recruitment was 28% with a slight initial upward trend with time. This was followed by a clear downward trend in HT use starting in July 2002, coinciding with the publication of the WHI interim results. From February to September 2005, the proportion of women using HT was between 10-11% (averaged 10.9%). The downward trend was confirmed in the age-adjusted proportion (with 95% confidence intervals) of women randomised per month using HT at recruitment for the entire study

period (Figure 13-17)). For all age groups, there was a decline in HT use from July 2002, although this decline was less pronounced for women over the age of 65. There was reduction in HT use with increasing age.

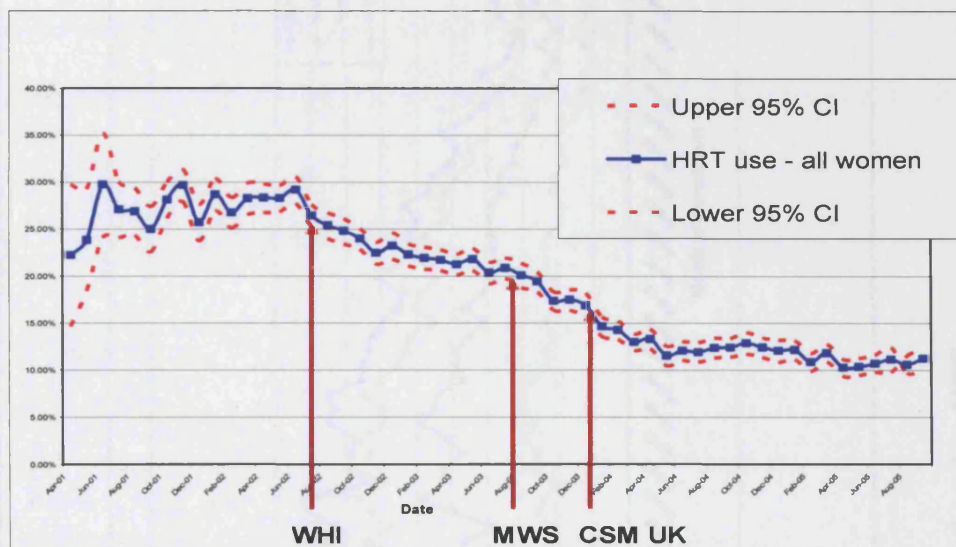


Figure 14-11: Proportion of women randomised each year using HRT in the birth cohorts and proportion randomised each month in each age group using HRT

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Figure 14-12: Percentage of women randomised each month using HRT

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Women with a personal history of ovarian cancer were ineligible for participation in the trial. 6% of women had previously had a cancer other than ovary or skin with 3.78% of women reporting previous breast cancer. 4.53% of women had a family history of ovarian cancer with 1.56% having mothers who suffered from the disease. 22.2% had a family history of breast cancer with a maternal history of breast cancer noted in 6.41% (Table 14-3).

Total number of women	202638 women	
	No of women	%
Hysterectomy	38210	18.86%
Tubal ligation	43135	21.29%
Fertility treatment	6629	3.27%
OCP use	120737	59.58%
Current HRT use	38002	18.75%
Personal history of cancer	12094	5.97%
Breast cancer	7658	3.78%
Bowel cancer	773	0.38%
Lung cancer	106	0.05%
Other cancer	3557	1.76%
Maternal history of cancer	16025	
Ovarian cancer - mother	3035	1.50%
Breast cancer -mother	12863	6.35%
Mother - both	127	0.06%
Family history of ovarian cancer	9186	4.53%
Relatives with Ovarian Cancer		
1	9029	4.46%
2	143	0.07%
>2	14	0.01%
Family history of breast cancer	44992	22.20%
No of relatives with breast cancer		
1	36965	18.24%
2	6460	3.19%
>2	1585	0.78%

Table 14-3 : Gynaecological history and personal and family history of cancer

All mandatory data fields were complete in women randomised to the trial. Table 14-4 shows the percentage of missing information in each of the non-mandatory data fields. This ranges between 0.16 (country of birth) to 1.5% (years of pill use). A variety of criteria used to estimate erroneous data, suggests that it is about 0.5% (Table 14-5). On checking recruitment data sheets, majority of the 278 women who stated their first period occurred over the age of 19, had entered in this field the age at their last period.

Non mandatory fields on the recruitment data sheet	No of women with missing data (%)
Ethnicity	1043 (0.51)
Years of Pill use in 120737 who noted they had used OCP	1811 (1.5)
Pregnancies <6 months	2674 (1.32)
Pregnancies >6 months	596 (0.29)
Age at first period	1083 (0.53)
Country of birth	318 (0.16)
Height	502 (0.52)
Weight	765 (0.38)

Table 14-4: No of women with missing data in the non mandatory fields in the recruitment data sheet

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Data fields on recruitment datasheet	No with possible erroneous data	Total (No randomised - No with missing data)	% error	Reason data considered possibly erroneous
No of Pregnancies <6 months	7	199964	0.004	No of entries with over 12 in this category
No of Pregnancies >6 months	21	202042	0.01	No of entries with over 12 in this category
Age at first period*	322	201555	0.16	<8 years and >19 - some of this data is correct
Height	818	202136	0.4	>210 cms and <120 cms
Weight	853	201873	0.42	<40kgs and >140kgs
Yrs of HRT use	48	38002	0.13	In those who admitted to HRT use, usage for >40 years
Yrs from LMP	346	202634	0.17	Yrs from LMP greater than 50 yrs or before born

All weights over 180kg and less than 30kg, heights over 210cm and less than 75cm and pregnancies > 12 have been checked against the recruitment questionnaire and any data entry errors have been corrected.

*For the erroneous age at first period, majority of the women have filled in their age at last period

Table 14-5: No of women with possibly erroneous data in the non-mandatory fields in the recruitment data sheet

14.4 Discussion

202,638 postmenopausal women aged 50-74 years from the general population residing in 27 participating primary care trusts in England, Wales and Northern Ireland volunteered to participate in UKCTOCS and were randomised. The baseline data collected at recruitment in this large national cohort of women provides useful information about trends in older women in the UK. However, it is important to note that this cohort consists of women willing to participate in an RCT of ovarian cancer screening. Women who volunteer to participate in research are usually more educated and informed¹⁷⁴⁻¹⁷⁶. Less important, as a result of exclusion criteria of the trial, the cohort does not contain women who have had bilateral oophorectomy, previous ovarian cancer, an active malignancy or who are at risk of familial ovarian cancer.

The median age was 60.6 years with 11% over the age of 70. The mean age of women recruited to the Million Women Study (MWS), a large UK based general population questionnaire study was lower (57.4 years) as the study involved recruitment through the NHS breast screening programme of women aged 50 to 64 years.¹⁸² Women participating in the Women's Health Initiative, an RCT of HRT based in the US had a mean age of 63.3+/- 7.1, again reflecting the eligibility criterion which was age 50 - 79 years.¹⁸³ The age differences are important when comparing baseline data between these studies.

In UKCTOCS, 7.4% of participants were born outside the UK which compares well with UK census data from April 2001 which reported that 8.3% of the population was born overseas (www.statistics.gov.uk). 96.4% of the women were white versus 92.1% of the population in the 2001 census (www.statistics.gov.uk). Black Caribbeans and Indians were the next largest ethnic groups. Most of the non white population were recruited from the London centres. Resources were not available for specific efforts to encourage greater participation of women from ethnic minorities. The trial design involved inviting women and since over 1.2 million women were sent invitations, it was not possible to use a language other than English. Interpreters were arranged to facilitate recruitment but women needed to inform the centre ahead of the appointment. Ethnicity was not recorded in the MWS. But in the WHI study, where special efforts were made to recruit women from ethnic minorities by publicising the trial in ethnic newspapers, newsletters, television and radio channels, 18.5 % of participants were from ethnic minorities (versus 20% in the US population).¹⁸³ There is increasing evidence that racial and ethnic minorities are as willing as whites to participate in health research. What is required are steps to ensure that all groups have greater access to health research, rather than try to change minority attitudes.¹⁸⁴ This was also noted in the Birmingham Rehabilitation Uptake Maximisation (BRUM) study, an RCT comparing a home-based with a hospital-based cardiac rehabilitation programme. Significantly more patients of South Asian ethnicity were excluded as they were ineligible based on language (i.e. the inability to speak English or Punjabi).

However, of those eligible, similar proportions were recruited from the different ethnic groups (white, South Asian and other). The primary reason for ineligibility was the inability to support the range of minority languages.¹⁸⁵ However they have been reports that trials that included an invasive arm enrolled fewer minority participants than expected.¹⁸⁶

Median self reported height of the trial participants was 163 cms and median weight was 66 kgs. The correlation between BMI based on self-reported height and weight and that based on measured height and weight is typically greater than 0.9.¹⁸⁷ The median body mass index in the trial was 25.8. Overall 37% of the women were overweight (BMI ≥ 25) and 21% were obese (BMI > 30) as per WHO criteria.¹⁸⁸ Although these figures are high, the UKCTOCS cohort seems to be less obese than the UK population. 31% of women in UK aged 55 to 64 are reported to be obese¹⁸⁹ when compared to 20.7% of UKCTOCS women in the same age group. There was little change in BMI patterns between the birth cohorts and in women grouped by age. In the WHI clinical trial, three quarters of the women were overweight or obese. The problems of overweight and obesity have achieved global recognition only during the past 10 years.¹⁹⁰ It is now well established that obese persons have diminished life expectancy. New evidence is emerging that even moderate elevations in BMI confer an increased risk of death. The risk of death in participants in the US NIH–AARP Diet and Health Study who were overweight at the age of 50 was 20 to 40 percent higher than that of those who had a normal BMI at that age.¹⁹¹ It will be possible in due course to estimate the impact of BMI on mortality in the UKCTOCS cohort.

Between the birth cohorts, there are clear differences in the reproductive choices that these women made, with earlier birth cohorts reporting less use of the pill, more viable pregnancies, fewer pregnancies <6 months and a lower rate of tubal ligation. While the absolute rates cannot be extrapolated to the general population, the differences between the birth cohorts in this large cohort of women are probably reflective of trends in the population.

18.9% of women had undergone hysterectomy with conservation of at least one ovary. At first glance, this is lower than the 25.1% hysterectomy rate noted in the Million Women Study (MWS). However once account is taken of the 7.4% of women in MWS who reported having undergone bilateral oophorectomy, the rates are remarkably similar.¹⁸² The Royal College of Obstetrics and Gynaecology estimates that 20% of women in the UK have a hysterectomy usually for benign conditions by the age of sixty.¹⁹² When the UKCTOCS birth cohorts were examined separately and over time, in women born in 1950-55, the hysterectomy rate at recruitment fell steadily from about 28.5% in 2001 to 16.3% in 2005 (Figure 14-8). In the eighties the hysterectomy trends were increasing. From 1987 to 1992 in Finland the hysterectomy rate increased by 22%, from 340 to 414 per 100,000 females.¹⁹³ However since then the hysterectomy rates for benign indications has been declining as a result of better medical management of menorrhagia using oral medication and the hormone-releasing intrauterine system and conservative surgical options for a variety of benign conditions. In California, there has been a significant decline, in the hysterectomy rates

for benign indications from 4.01 per 1,000 women in 1994 to 3.41 per 1,000 women in 2003¹⁹⁴ while in Western Australia, the age-standardised hysterectomy rate decreased 23% from 6.6 per 1000 woman-years in 1981 to 4.8 per 1000 woman-years in 2003. The age when the UKCTOCS women underwent hysterectomy was not elicited. In the UK VALUE survey of hysterectomies, the median age at hysterectomy (both with and without conservation of ovaries) was found to be 45, with dysfunctional uterine bleeding being the most common indication.¹⁹⁵ Given that the hysterectomies in the UKCTOCS women were for benign disease and associated with conservation of at least one ovary, it can be surmised that the majority of the women may have undergone the operation prior to their mid forties. Women in the birth cohort 1950-55 would have been in their early forties in the 1990s and the decreasing hysterectomy rates noted in this birth cohort are probably a reflection of the international trends.

137,059 women were neither on HRT at recruitment nor had undergone a hysterectomy. The median age at natural menopause in this group was 50.5 years (25th, 75th quartiles 48 and 52.95). This is in keeping with the estimated average age at natural menopause in Western countries of between 50 and 51 years.¹⁹⁶ Recent estimates from various countries have ranged from median age at natural menopause in Puerto Rico of 51.3 years¹⁹⁷, in Spain of 51.7 years, and in the U.S. of 52.6 years.¹⁹⁸ A more detailed analysis of the effects of parity, deprivation and other factors on menopausal age should be possible.

The proportion of women using HT at recruitment was 29% between April 2001 and June 2002. However from July 2002 there was a steady decline in women using HT and by February 2005 to September 2005 only 10-11% of newly recruited women were using HT. While the absolute rates of HT use may not apply to the UK female population, given the large size of this national cohort and the pronounced decline in HT use, the trend observed is probably representative of a general trend in the UK. This cohort of women seem similar in current HT use to those who participated in the MWS. In MWS women were recruited between 1996 and 2001 and the overall rate of current HT use at recruitment was 33%¹⁹⁹ which is similar to the 35% overall rate of current HT use in postmenopausal women aged 50-64 recruited in 2001 to UKCTOCS. The cohort itself was fairly homogenous as there was no change over time in the proportion of recruited women with a personal history of breast cancer, number of relatives with breast or ovarian cancer or hysterectomy. As variation in the proportion of women in various age groups over time could impact on HT use, the age groups were examined separately. The decline in HT use from July 2002 was present in all age groups.

Similar downward trends have been reported from the USA²⁰⁰⁻²⁰² and Europe²⁰³⁻²⁰⁵ in the period 2002-2003 immediately following publication of the trial results. Studies reported a decline in HT prescribing in the USA from 14.6% in September 1999 to 7.9% in June 2002 in women aged 40-80 years²⁰²; The Netherlands from 10.7% in 2000 to 8.7% in 2003 in women aged 45-69 years²⁰³ and in Hong Kong from 12.2% in the second half of

2000 to 4.5% by the first half of 2003 in women aged 50 or above²⁰⁶. In an observational cohort study of postmenopausal US women aged 50-74 undergoing mammography an 18% decline in HT use per quarter was documented during July 2002 and May 2003²⁰¹. The UKCTOCS data shows a smaller rate of decline in the UK, but one that continued to fall until February 2005 when it stabilized. An annual report on prescription costs for England by the Department of Health support these findings. In 2001, there were 6.3 million HT prescriptions dispensed in England and by 2004, this had fallen to 3.8 million²⁰⁷.

The timelines suggest that the decline is related to the publication of the WHI and MWS results. In the USA, the dissemination of the WHI HT trial results had an immediate impact on the discontinuation of HT²⁰⁰. Our data suggests that in the UK, the publication of the US study was followed by a gradual decline in HT use which fell more steeply after publication of the British MWS in August 2003. The difference in impact of the two trials on HT use was also noted in the Netherlands with a modest decline in HT prescribing after the publication of the WHI study, followed by a dramatic fall in the prescribing of HT after release of results from the MWS²⁰³.

Reports from small longitudinal cohort studies support the decline in HT use to be related to the WHI trial^{208 209}. The decline was, however less pronounced in Germany where in a survey of 8,380 women (mean age 56.1 years) only 25.7% reported stopping HT in response to the WHI results²¹⁰ as

opposed to 40% and 60% in the reports from New Zealand²⁰⁹ and USA²⁰⁸ respectively.

A number of factors may have contributed to this decline. Media coverage of the WHI study had a significant influence on women's use of HT²¹¹. There was a misunderstanding about the magnitude of risks and benefits. The original publication and most of the ensuing publicity from WHI phrased the risks as a percent increase (or decrease) of the relative risk. For example, there was a 24% increased relative risk of breast cancer per year in the HT group. The general public, not understanding the concept of relative risk, interpreted this statement as a 24% chance of developing breast cancer each year on HT²¹². An evaluation study of educational intervention on HT continuation rate in Slovenia confirmed that the main reason for discontinuing HT was fear of breast cancer, intensified by the media²¹³. A recent Cochrane review identified five studies that evaluated health care utilization before and after media coverage of specific events²¹⁴. Each found changes in utilization: favourable publicity was associated with higher use, unfavourable publicity with lower use. The Cochrane review concluded that media reports played an important role in influencing the public's use of health care interventions. Media coverage as distinct from the scientific importance of the work also plays an important role in transmitting knowledge to the scientific community²¹⁵. In addition, guidance circulated by most health care providers about the implications for prescribing HT probably contributed to the observed changes²¹⁶ as did the advice given by physicians as women who continued to taking HT did so largely based on

their physician's advice²¹⁷. Interrelated with all of this, reduced promotion of HT by the pharmaceutical companies may have further played a role in the decline in prescriptions²¹⁸.

The large cohort size makes it possible to explore numerous other variables. However, in an effort to maintain the focus of the trial, ensure good quality data and complete recruitment in the stipulated time period, we have not captured detailed medical history or information on lifestyle and socio-demographic factors. More information is being collected via the follow up questionnaires which women receive in the course of the trial and this should make it address issues that are more specific.

15 SUMMARY

This thesis spans work done over eight years from June 1997 to December 2005. A lot has been achieved during this long journey and the stage is now set to definitively answer the question – Will ovarian cancer screening save lives?’

The first step involved literature review and refining the ROC algorithm using ultrasound data from the initial trial of 22,000 women. There were 1219 scans available from 741 women who underwent a second line test due to a serum CA125 measurement of ≥ 30 U/l. A database was built, a classification system proposed, data entry mostly from hand written cards supervised, missing outcomes chased by writing to GPs and doctors, data repeatedly audited and finally analysis done. This resulted in alteration of the ROC algorithm so that ovarian morphology was used instead of volume to interpret scans.

At this point the pilot RCT of 13,582 postmenopausal women was underway and the refined ROC algorithm incorporating the new ultrasound criteria was implemented. Day to day work involved managing the women detected to have screen abnormalities on the trial and addressing the various logistic issues involved in running the pilot RCT. Collection of outcome data involved follow up postal questionnaires to all 22,000 women. Preliminary analysis revealed that screening with the ROC algorithm was feasible and could achieve high specificity and positive predictive value. This data was

SUMMARY

used to inform the UKCTOCS trial design. Final analysis of the prevalence screening was completed and published in 2005.

Meanwhile in 1999, work was underway writing a project grant to the MRC, CRUK, and Department of Health for a definitive ovarian cancer screening RCT of 200,000 women. It was decided this should include a head to head comparison of both OCS strategies - multimodal and ultrasound. Specific aspects that were the remit of the researcher were literature review; the screening strategy in the ultrasound arm, estimating outcomes based on known performance characteristics of the screening strategies and detailed planning of the logistics of the proposed trial. The grant was awarded in 2000 and as trial coordinator implementation of the project was the researcher's remit.

The trial was set up between late 2000 and 2002. Tasks involved:

- 1) Writing up the detailed trial protocol and numerous standard operating procedures for each aspect of the trial from labelling samples to surgery.
- 2) Setting up transparent, robust and sustainable financial processes for managing the grant income; accurate forecasting of expenditure as it evolved and changed over the course of the 12 years of the trial.
- 3) Separate negotiations with the Department of Health to finalise a process for efficient transfer of subvention to the RCs.

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- 4) Negotiation with the lead researchers of initially 17 Trusts. This involved drawing up and providing accurate forecasts for finances, staffing, space and support for the duration of the trial that leads could use to negotiate with their Trust Boards. Finally 13 RCs were set up. In 2000, there were no standard contracts or processes and these had to be drafted and legal advice sought.
- 5) Approval from MREC, 13 LRECs and 13 R&D departments.
- 6) Approval from Caldicott guardians from 27 PCTs for permission to use data from their age sex registers to invite the women.
- 7) Approval for the flagging study from the ethics committees of the Office of National Statistics for England and Wales and protracted negotiations for the same for Northern Ireland which lasted almost six years.
- 8) Recruitment and training of the coordinating centre team which was built up from 3 [Prof Jacobs, the trial manager and the researcher] to the current 20 – this involved writing job descriptions, advertising, short listing, appointing, induction and training. In the first two years, there was significant turn over of clerical, nursing and laboratory staff. In addition, the trial manager who had been involved in the pilot RCT left and moved abroad.
- 9) Setting up of a new laboratory for processing and analysing the blood samples
- 10) Changing the method of analysis of serum CA125 - It was clear that it would not be possible to analyse the large number of samples for serum CA125 using the original radioimmunoassay. The

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introduction of an enzyme linked immunoassay using a semi automated platform meant that 6000 samples from the pilot RCT had to be re-assayed so that a correction factor could be calculated for incorporation into the ROC algorithm.

- 11) Setting up a novel system for storage of the serum. Various options were explored to ensure high throughput, maximum efficiency and long term viability of the samples for future research. Finally a semi automated system using straws and storing the samples in liquid nitrogen tanks was set up. In the initial phase there were numerous training issues and problems with using the system.
- 12) Setting up a cryostore of liquid nitrogen tanks. This turned out to be a huge issue for the first 5 years due to the problems with space. Lateral thinking and intense negotiations with Estates led to a temporary solution through building a large shed on the QMUL college grounds. In 2004 on transfer of the CC to UCL, this task was handed over to a commercial organisation with off site storage facilities.
- 13) Assisting the RC leads with setting up the local centres and recruiting, and training the staff.
- 14) Setting up the logistics of daily transport of blood samples from the 13 RCs to the coordinating centre laboratory, weekly transfer of all documentation to and from the RCs, regular delivery of consumables including venepuncture equipment to RCs.
- 15) Putting in place high throughput procedures for sending out thousands of letters to women every day. This involved

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- procurement of high specification printers, a machine for stuffing envelopes, a franking machine and contracts with the Royal Mail.
- 16) Tendering in Europe for 13 ultrasound machines and going through a detailed procurement process. Writing up the tender documents was one of the most challenging tasks faced.
 - 17) Organising maintenance contracts for the core equipment
 - 18) Organising the printing and delivery of thousands of trial brochures, patient information sheets, and site-specific consent forms. The challenge was in getting the lowest price which meant large volumes but working within the constraints of storage space.
 - 19) Writing the transcript and assisting in the shooting and editing of the trial information video
 - 20) Setting up of the various overseeing committees - DMEC, TSC and Outcomes Committee, all of whom had independent members who needed to be updated on a regular basis on study progress.
 - 21) Setting up the database management system that underpins all of UKCTOCS. The DMS was built by a commercial organisation but input from the researcher was significant. The technical specification document alone that was drawn up ran into hundreds of pages. The system was tested at each stage as it was built and arrangements made for data from various sources such as the Office of National Statistics, PCTs, the CA125 analyser to be directly uploaded into the system
 - 22) Setting up of data transfer between the main UKCTOCS trial and the Psychosocial Study at the University of Sussex.

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- 23) Organisation of publicity as the main trial and then each of the centres went live. This required coordination with various funding agencies and Trust press officers to ensure everyone was aware and there were processes in place to handle the ensuing enquiries.
- 24) Putting in place robust procedures for documenting and responding to complaints and reporting adverse events.

In addition, the researcher directly set up and ran the RC at Barts and the London which involved a whole series of separate tasks - local negotiations, recruiting staff, managing the logistics and being directly involved in the clinical assessment of women from this centre.

Recruitment commenced in April 2001 with 13 RCs set up in a staggered fashion. This phase involved continuous monitoring of targets to ensure issues were addressed in real time, fine-tuning of invitation rates and appointments to accommodate regional variations in response and attendance respectively, site visits to RCs to help resolve various issues that arose in the initial phase, organisation of team meetings and continuously working on team building and motivation. The DMS was repeatedly refined in response to new needs and the operating protocols regularly revised. In response to new MRC guidelines on consent, patient information and consent forms were revised and 50,000 women who had been randomised contacted again to clarify further issues with regard to ONS flagging, secondary studies and stored samples. In April 2004, the department moved from QMUL to UCL. Many of the processes that were in place, had to be set

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up again especially documentation, contracts, and logistics of transport. The biggest task was setting up a new laboratory. However, by this time an extremely competent laboratory manager was in post who took over the brunt of this task.

1248453 invitations were sent. 31% of women accepted the invitation. The acceptance rate varied between 24% in East London (Bart's) to 38% at Portsmouth. Between April 2001 and September 2005, 205,208 women attended for recruitment. 202,638 participants were randomised to the trial, making it the largest randomised control trial ever undertaken. 10189 women could not be recruited into the trial despite wishing to take part as the recruitment target was met.

Good quality data with minimal errors or missing information was collected at recruitment. Analysis of this data revealed a wealth of information both about trends in use of reproductive options like the oral contraceptive pill, tubal ligation in women belonging to different birth cohorts as well as trends in practices like HRT use which changed over the course of the recruitment period.

16 FUTURE DIRECTIONS

The UKCTOCS trial is poised to answer the crucial question of whether screening can impact on ovarian cancer mortality. The focus in the next 5 years is to ensure that annual screening continues to be organised efficiently and high levels of compliance are maintained. It is anticipated that the first results will be available in 2012 when each woman has been in the trial for 7 years post randomisation. Once a mortality impact is established, detailed information collected on compliance, cost, psychological and physical morbidity and the performance characteristics of the two screening strategies will provide the basis for the NHS to implement an OCS programme.

One of the main challenges in setting up any screening programme is quality assurance. This is especially an issue when the strategy involves screening tests such as ultrasound which have a definite subjective element. Work is underway to develop a well defined rigorous and sustainable quality assurance programme for ovarian ultrasound together with a web based training and accreditation process. The work is the basis of a future PhD which the researcher is supervising.

The serum bank together with follow up of all women in UKCTOCS via the Office of National Statistics provides unique opportunities to improve on the currently available tests through discovery of novel biomarkers for cancer screening. Well characterized serum samples are now available from

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women many years ahead of their cancer diagnosis. Projects already underway include

- 1) An MRC funded biomarker discovery project using a variety of proteomic technologies for early detection of ovarian, breast, and other cancers. This involves collaborations with the proteomics group in UCL, Reading University and National Cancer Institute laboratories in Washington, US and bioinformatics support from the computer science department at Royal Holloway University, UK.
- 2) An NIH funded project in collaboration with Pittsburgh University in the US using high through put multiplex antibody assays to explore use of marker panels for screening for ovarian and pancreatic cancer.

Integral to any screening programme is defining the target population with increased disease prevalence increasing the positive predictive value of the screening strategy. The data collected from women in the UKCTOCS cohort together with the serum samples provides the opportunity to refine risk assessment in the general population. Projects are underway to predict risk for ovarian and breast cancer using novel strategies which include assessment of free circulating methylated DNA in the serum. This work is based on an entirely new model of carcinogenesis proposed by the group i.e. that tumour cells arise from stem cells whose potential to differentiate has been irreversibly destroyed by means of CpG island methylation and that high cell turnover and lysis leads to this hypermethylated tumour-derived DNA in the blood stream.^{219 220} Work is also underway to built risk

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prediction models for breast and endometrial cancer using hormone profile including oestrogen bioactivity and ultrasound data of ovarian size and endometrial thickness and morphology.

In addition, the plan is to approach women in the multimodal arm of UKCTOCS who have a blood test every year for consent to store DNA. This germline DNA would enable further refinement of risk prediction using single nucleotide polymorphisms for a number of common diseases. An international consortium (The Ovarian Cancer Association Consortium) has been set-up by the researchers involving 15 groups across USA, Europe, and Australia for a case control study involving 10,000 ovarian cancer patients and matched controls. It is anticipated that UKCTOCS would contribute towards this and other similar efforts to assess risk in common cancers like breast and colon as well as common diseases such as coronary heart disease.

The cohort also provides a unique opportunity to prospectively explore the role of symptoms in ovarian cancer by carrying out a symptom survey of the entire cohort. An MRC studentship has been awarded for this and a large study is being designed. Projects to further explore some of the findings noted in this thesis are also underway such as survey on management of menopausal symptoms given the falling trend noted in the UKCTOCS cohort of HRT use. Studies of risk prediction in other common diseases such as coronary heart disease are being explored.

17 PUBLICATIONS / PRESENTATIONS

17.1 Peer reviewed articles

1. Jacobs IJ, Skates SJ, Macdonald N, Menon U, Rosenthal A, Davies AP, Woolas R, Jeyarajah A, Sibley K, Oram DH (1999). Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 353; 1207-10.
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17.2 Reviews and chapters

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- 6 Menon U, Jacobs IJ (2000). The current status of screening for ovarian cancer. *Current Medical Literature*.
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- 9 Menon U, Jacobs IJ (2001). Ovarian cancer screening in the general population– current status. *International Journal Gynecological Cancer*.11(S1):3-6.
- 10 Menon U and Jacobs IJ (2002). Screening for ovarian cancer . In S Arulkumaran *Baillière's Best Practice & Research Clinical Obstetrics & Gynaecology*; London. 2 Aug;16(4):469-82.
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- 19 Menon U, Jacobs IJ (2005) Serum tumour markers. In: Smith JR, Priore GD, Curtin J, Monaghan J, eds. *An atlas of gynaecological oncology*. London: Martin Dunitz. 21-43.

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- 21 Sharma A, Menon U (2006). Screening for Gynaecological Cancers *European Journal of Surgical Oncology* May 6

- 22 Adam Rosenthal, Usha Menon, Ian Jacobs (2006). Ovarian Cancer Screening. In Reznick R eds. *Contemporary Issues in Cancer Imaging: A Multidisciplinary Approach*. Cambridge University Press, 2006 (in press).

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17.3 Oral presentations / published abstracts

The role of ultrasonography in a multimodal screening strategy for ovarian cancer. Poster at British Gynaecological Cancer Society Annual Meeting at Bristol on 8th Nov, 1997.

The role of ultrasonography in a multimodal screening strategy for ovarian cancer. William Harvey Day, St Bartholomew's and the Royal London School of Medicine and Dentistry at London on 20th Oct, 1998.

Risk of Ovarian Cancer Algorithm (ROCA) for the Early Detection of Ovarian Cancer XXVIII International Society for Oncodevelopmental Biology Meeting at Munich on 9th September 2000

Screening for Ovarian Cancer National Screening Committee Meeting on Screening for late onset genetic disorders – breast ovarian cancer at Cardiff on 10th November 2000.

Further thoughts on ovarian cancer screening Gynaecological Oncology meeting - Cervical and Ovarian Cancer at St George's Hospital Medical School on 24th November 2000

Developments in screening and preoperative diagnosis of ovarian cancer at Regional Scientific Meeting of Association of Clinical Biochemists at Edinburgh on 6th March 2001

PUBLICATIONS / PRESENTATIONS

Screening for Ovarian Cancer Principle and practice of screening in obstetrics and gynaecology at North West Wales NHS Trust on 30th March 2001.

Screening for Ovarian Cancer Gynaecological Ultrasound Course at Royal College of Obstetricians and Gynaecologists on 19th September 2001.

Screening for Ovarian Cancer The silent disease – Ovarian Cancer at the Royal Surrey County Hospital NHS Trust on 24th September 2001

Sonography in ovarian cancer screening - Review and update of ongoing trials at 4th Annual International Ovarian Cancer Screening Meeting at Fred Hutchinson Cancer Research Centre, Seattle on 7th November 2001.

Evaluation of sonography data in ovarian cancer screening trials 4th Annual International Ovarian Cancer Screening Meeting at Fred Hutchinson Cancer Research Centre, Seattle on 7th November 2001.

Screening for Ovarian Cancer Screening in Gynaecological Oncology at Sint-Augustine Hospital, Antwerp on 7th November 2001.

Screening for Ovarian Cancer European Society of Urogenital Radiology at Genoa on 17th June 2002

PUBLICATIONS / PRESENTATIONS

Screening for Ovarian Cancer Key advances in the effective management of Ovarian Cancer at Royal College of Physicians 2002

Ovarian cancer screening 4th Ovarian Cancer Research Symposium at Swedish Medical Centre, Seattle on 19th September 2002.

Progress in Screening for Ovarian Cancer All India Congress of Obstetrics and Gynaecology at Bangalore on 8th January 2003.

Current ovarian cancer screening trials Helene Harris Memorial Trust Meeting at Stratford on Avon on 27th March 2003

Prevalence screening for ovarian cancer using Risk of Ovarian Cancer Algorithm European Society of Gynaecological Oncology at Brussels on 7th April 2003.

Screening for Ovarian Cancer at the Gynaecology Nursing Forum Conference of Royal College of Nursing at Leeds on 8th May 2003.

Screening for Ovarian Cancer – Current Trials at the Annual Joint Gynaecology Oncology Meeting at Institute of Molecular Medicine at Oxford on 15th October 2003.

PUBLICATIONS / PRESENTATIONS

United Kingdom Familial Ovarian Cancer Screening Study at Annual Meeting of the Traveller's Society at Bart's and the London NHS Trust on 3rd Nov 2003.

Screening for Sporadic Ovarian Cancer at the 13th Annual Meeting in Honour of Professor Per Kolstad, Norwegian Radium Hospital, Oslo on 5th Dec 2003.

Will ovarian cancer screening save lives? at 25th Anniversary Meeting of British Gynaecological Cancer Society at Royal College of Obstetricians and Gynaecologists on 20th May 2004.

UK Collaborative Trial of Ovarian Cancer Screening at the 10th Biennial IGCS Meeting at Edinburgh on 3rd Oct 2004.

Ovarian cancer Will screening impact on mortality? at The Practical Management of Ovarian Cancer meeting at London on 9th March 2005.

Ovarian Cancer Screening Trials at the Cancer Ideas Workshop at University College London on 21st April 2005.

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